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NEW EVIDENCE
VOL. XII NO. 1 (Pp. 161–320)
Circulation
September 1955 THE AMERICAN JOURNAL of the MEDICAL SCIENCES Vol 230, No.
AMERICAN HEART JOURNAL

How you can prevent attacks of angina pectoris

Three new studies have recently been added to the extensive investigation of Peritrate's effectiveness in preventing attacks of angina pectoris:

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1. Binder, M. J., et al.: **Am. Jour. Med.,** 18:622, Apr., 1955. **2.** Sampson, J. J.; and Zipser, Albert: **Circulation,** 9:38, Jan., 1954. **3.** Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. **4.** Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.,** 3:521, Aug., 1955. **5.** Gilchrist, A. Rae: **Brit. Med. Jour.,** 2:351, Aug. 16, 1952.

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Vol. XX MARCH, 1956 No. 3

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Ebstein's Disease . . JAMES W. BROWN, DONALD HEATH AND WILLIAM WHITAKER 322

The congenital anomaly of the tricuspid valve described by Ebstein is apt to cause confusion in diagnosis but with modern technics the diagnosis now can be made with assurance during life. The present report concisely describes the findings in four such cases, two with necropsy, and thus, in view of the rarity of the disorder, adds substantially to present information regarding this anomaly. The authors further summarize the total experience in the literature concerning Ebstein's disease, with special reference to symptoms and signs, and the available electrocardiographic, radiologic, angiocardiographic and cardiac catheterization data. A fairly distinctive clinical differentiation emerges.

Mechanism of A-V Arrhythmias. With an Electronic Analogue of the Human A-V Node ROBERT P. GRANT 334

In a perceptive analysis of the common A-V arrhythmias of acute rheumatic fever, Dr. Grant takes issue with the prevailing view that these are attributable to varying degrees of delay in conduction along the fibers of the A-V node. He proposes an alternative explanation, more consistent with modern excitation theory, based on the assumption of two electrical oscillators of different rates, one the P oscillator, the other a subthreshold nodal oscillator. When the two oscillators "pull in," fixed P-R interval prolongation is produced; when they pull apart, Wenckebach periods or A-V dissociation are produced. This mechanism, which appears neatly to explain the observed clinical phenomena, is illustrated by an electronic analogue for the A-V node which, by graded change of a single parameter, reproduces the various A-V arrhythmias encountered in acute rheumatic fever.

Antemortem Diagnosis of Syphilitic Aneurysm of the Aortic Sinuses. Report of Nine Cases . . CHARLES W. MERTEN, NATHANIEL FINBY AND ISRAEL STEINBERG 345

Aneurysms of the aortic sinuses are rarely suspected during life, except perhaps at the time of rupture, and are even more rarely unequivocally demonstrated in the living patient. Angiocardiography now makes this demonstration possible. In an article of unusual interest the authors describe the clinical and roentgenographic features of syphilitic aneurysm of the aortic sinuses, as encountered in their nine cases (in six of these associated with fusiform dilatation of the ascending aorta) and in nineteen autopsied cases from the literature. It should be noted that such aneurysms are not incompatible with prolonged survival, even after rupture into the right heart or pulmonary artery.

Contents continued on page 5

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VOLUME TWENTY NUMBER THREE

Ventricular Septal Defect with Aortic Incompetence Simulating Patent Ductus Arteriosus . . . . . PAUL WINCHELL AND FOUAD BASHOUR 361

The authors call attention to the close similarity to patent ductus arteriosus of the findings presented by a small group of patients with high ventricular septal defect and downward displacement of an aortic cusp: a loud, left, apparently continuous (actually to and fro) parasternal murmur, increased pulmonary artery flow, increased systemic pulse pressure. The distinction usually can be made by catheterization studies. The authors cite examples of this interesting anomaly, which is associated with little functional incapacity until cardiac failure or bacterial endocarditis intervenes, and discuss the differential diagnosis.

Clinical and Pathologic Significance of Atheromatous Embolization, with Emphasis on an Etiology of Renal Hypertension . . . . . FRED P. HANDLER 366

There can be little doubt that the frequency and clinical significance of atheromatous embolization is not sufficiently appreciated, even by pathologists, who are apt to confine examination of postmortem tissue to sections obtained after the ordinary routines of fixation and staining. In the present study it is suggested that embolization of the kidneys in this way may eventuate in renal hypertension; the evidence, however, is too limited to be convincing, even if the principle is acceptable.

Idiopathic Pulmonary Hemosiderosis . . J. R. BROWNING AND JOHN D. HOUGHTON 374

Idiopathic pulmonary hemosiderosis is an obscure and puzzling disorder encountered chiefly in children but occasionally also in adults, as indicated by the three cases cited. The condition may readily cause confusion in diagnosis, so the brief account here recorded will be found of interest. The response to ACTH and cortisone in one case deserves further investigation.

Biliary Tract Studies. I. X-ray Diffraction Analysis of Gallstones; Correlation with Occurrence of Microspheroliths in Bile

KERRISON JUNIPER, JR. AND WILLIAM E. WOOLF 383

An interesting study of the composition and significance of microscopic crystalline structures, really miniature gallstones, with the potential for growth, not infrequently occurring in the bile. X-ray diffraction studies indicate that these microliths contain calcium (usually as the carbonate), calcium-pigment complexes and perhaps cholesterol. Large numbers of them are likely to be present in association with hemolytic anemia.

Therapy of the Malignant Lymphomas CHARLES A. HALL AND KENNETH B. OLSON

I. A Study of 116 Cases 392

II. A Review 399

The first paper summarizes the results of the authors' own experience in the treatment of 116 cases of malignant lymphoma (chiefly Hodgkin's disease and lymphosarcoma), for the most part by roentgenotherapy and/or nitrogen mustard. Their findings conform with the general experience that these two forms of treatment give essentially similar results in producing and maintaining remissions. In accordance with usual practice, the authors appear to have reserved nitrogen

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CONTENTS continued–March 1956

VOLUME TWENTY NUMBER THREE

mustard for use in patients with extensive or refractory lesions, and this selection of cases should be taken into account in the comparisons of treatment. The second paper attempts to correlate the data in the literature dealing with the effectiveness of surgery, roentgenotherapy, nitrogen mustard, TEM and other modalities in the management of the malignant lymphomas. Despite the insurmountable difficulties in making valid comparisons, the results of this study are of great interest. The authors plead for better standardization and organization of therapeutic regimens.

Clinical Trial of Glaucarubin in Treatment of Amebiasis
EFRÉN C. DEL POZO AND MANUEL ALCARAZ 412

The effects of a new drug, glaucarubin, in the treatment of seventy-eight cases of chronic amebiasis and nine patients with acute amebic infestation are described. The results are impressive but final evaluation must await additional experience and more careful analysis of the relapse rate and of toxicity in man.

Review

Serologic Tests for Inflammation. Serum Complement, C-reactive Protein and Erythrocyte Sedimentation Rate in Myocardial Infarction
ADOLPH J. BOLTAX AND EDWARD E. FISCHEL 418

There has been increasing interest in recent years in various non-specific tests of inflammation, other than the erythrocyte sedimentation rate, particularly in connection with their possible special usefulness in the management of myocardial infarction. The present study engages the same problem but from a broader and better balanced point of view than most previous investigations. A comparison of the results of serial determinations of erythrocyte sedimentation rate, serum complement (C′) and C-reactive protein in patients with myocardial infarction failed to establish any special virtue of the latter two more involved tests, although each has its own particular serologic significance and the results with all are by no means identical. Limited value of such tests in the detection of the more insidious complications of myocardial infarction has not been excluded.

Seminar on Allergy

Delayed Type of Allergic Inflammatory Response . . H. SHERWOOD LAWRENCE 428

Dr. Lawrence contributes this Seminar on allergy of the delayed type, a form of allergic inflammatory response which may follow infection with a variety of bacteria, viruses and fungi, as well as exposure to many chemical compounds. This type of allergy presents unusual problems to the immunologist because, although a specific immune response, neither specific antigen nor specific antibody can be detected in the blood or elsewhere. Transfer can be effected by appropriate injection of leukocytes or extracts thereof, an indication of the predominant role of cells in induction of this form of allergic inflammatory response. Many other interesting immunologic aspects are presented. Dr. Lawrence concludes with a section indicating the significance of allergy of the delayed type in various diseases, notably tuberculosis as a proved example and rheumatic fever as a probable one.

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*Verse by
RICHARD ARMOUR
Illustrations by
LEO HERSHFIELD

IGNORANCE ISN'T BLISS*

There is an awful, quite unlawful,
Violent and dread ache
That should have fame and Latin name
And yet is called "a headache."

The victim thinks his head's in kinks,
Or, from the inner clamor,
Some hidden sprite with all his might
Is banging with a hammer.

He seems to feel that rods of steel
Are thrusting through his cranium.
In state so vile, he couldn't smile
To hear he'd struck uranium.

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CONTENTS continued–March 1956

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Combined Staff Clinic

Disorders of Renal Tubular Function 448

Combined Staff Clinics (Columbia University College of Physicians and Surgeons)—This clinic deals with the manifold and complex operations of the renal tubules in their vital function of maintaining homeostasis and the disorders which result from inborn or acquired tubular abnormalities. The first section deals with the mechanisms of tubular reabsorption of glucose and the anomalies responsible for renal glycosuria. Then follows a discussion of tubular regulation of electrolyte and water excretion and conservation, with special emphasis on the central role of sodium-hydrogen ion exchange. The clinic closes with a consideration of the mechanisms and management of renal tubular acidosis and Fanconi syndrome.

Clinico-pathologic Conference

Arthritis, Polymyositis and Polyneuritis 462

Clinico-pathologic Conference (Washington University School of Medicine)

Case Report

Isolated Congenital Bicuspid Pulmonary Valve. Clinical and Pathologic Study

Amasa B. Ford, Herman K. Hellerstein, Colin Wood and Hugh B. Kelly 474

An excellent study of pulmonary insufficiency due to a rare congenital anomaly, isolated bicuspid pulmonary valve, diagnosed during life and confirmed at necropsy. The results of cardiac catheterization are included in the report. An account of the literature is given, together with a summary of the clinical and hemodynamic characteristics.

Advertising Index on 3rd Cover

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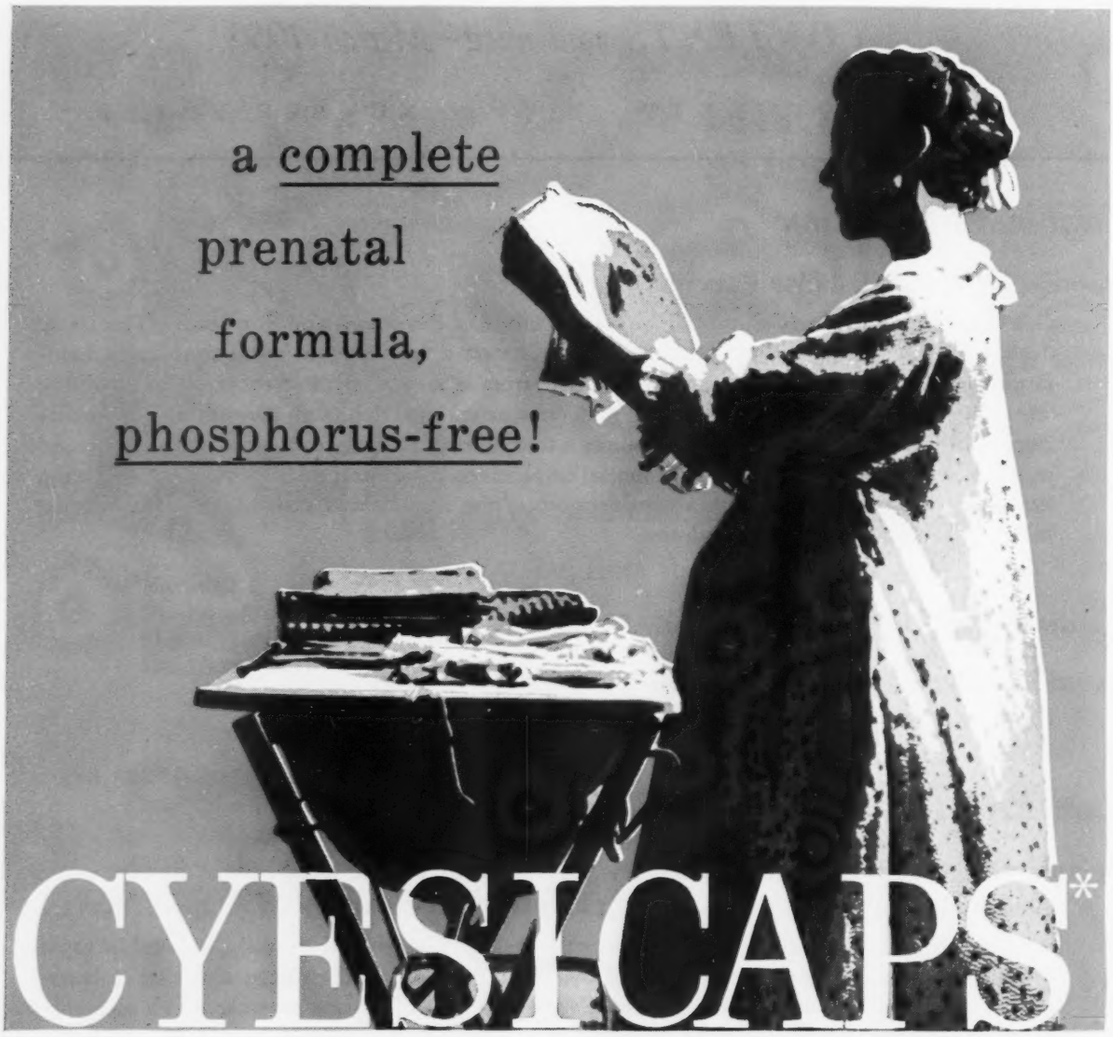

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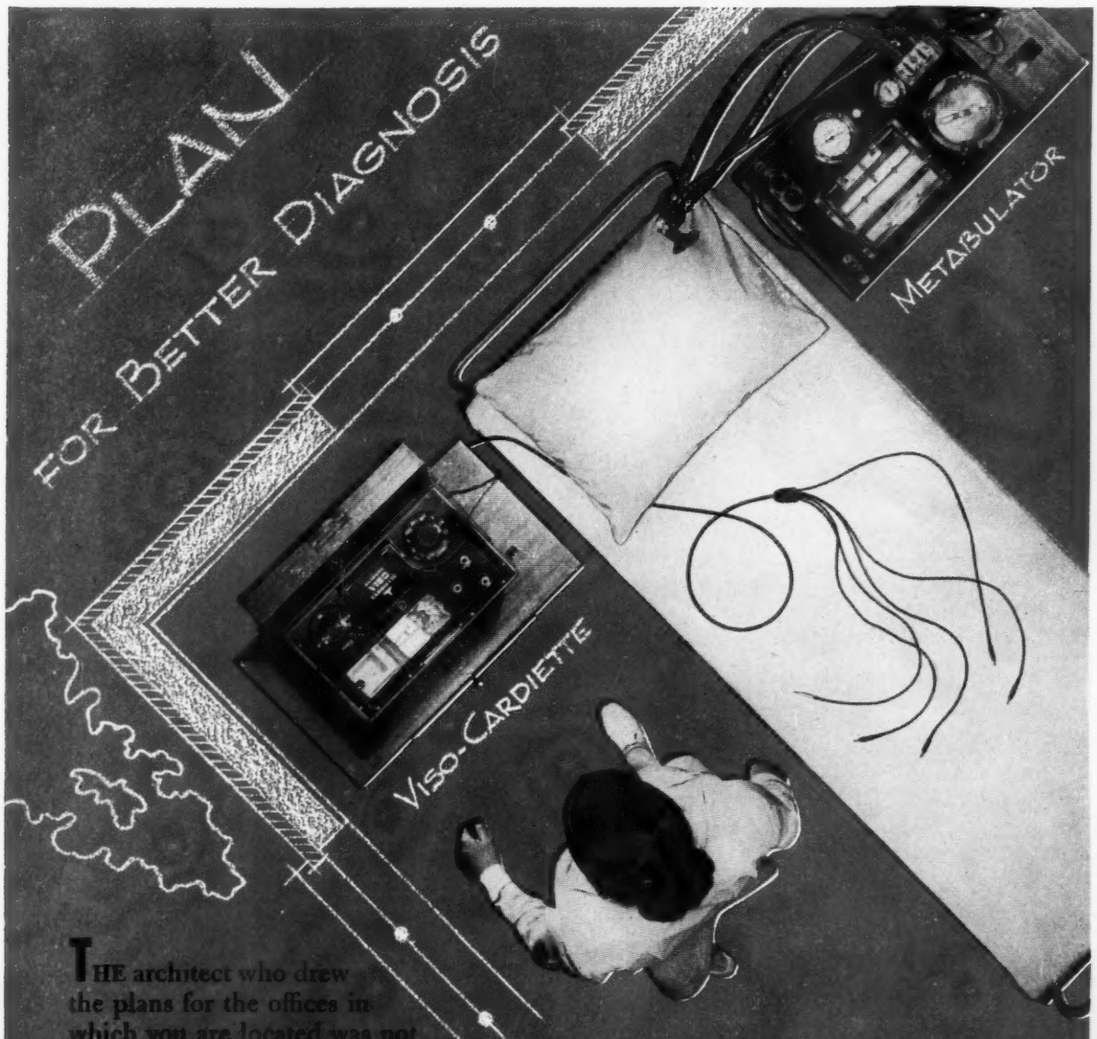

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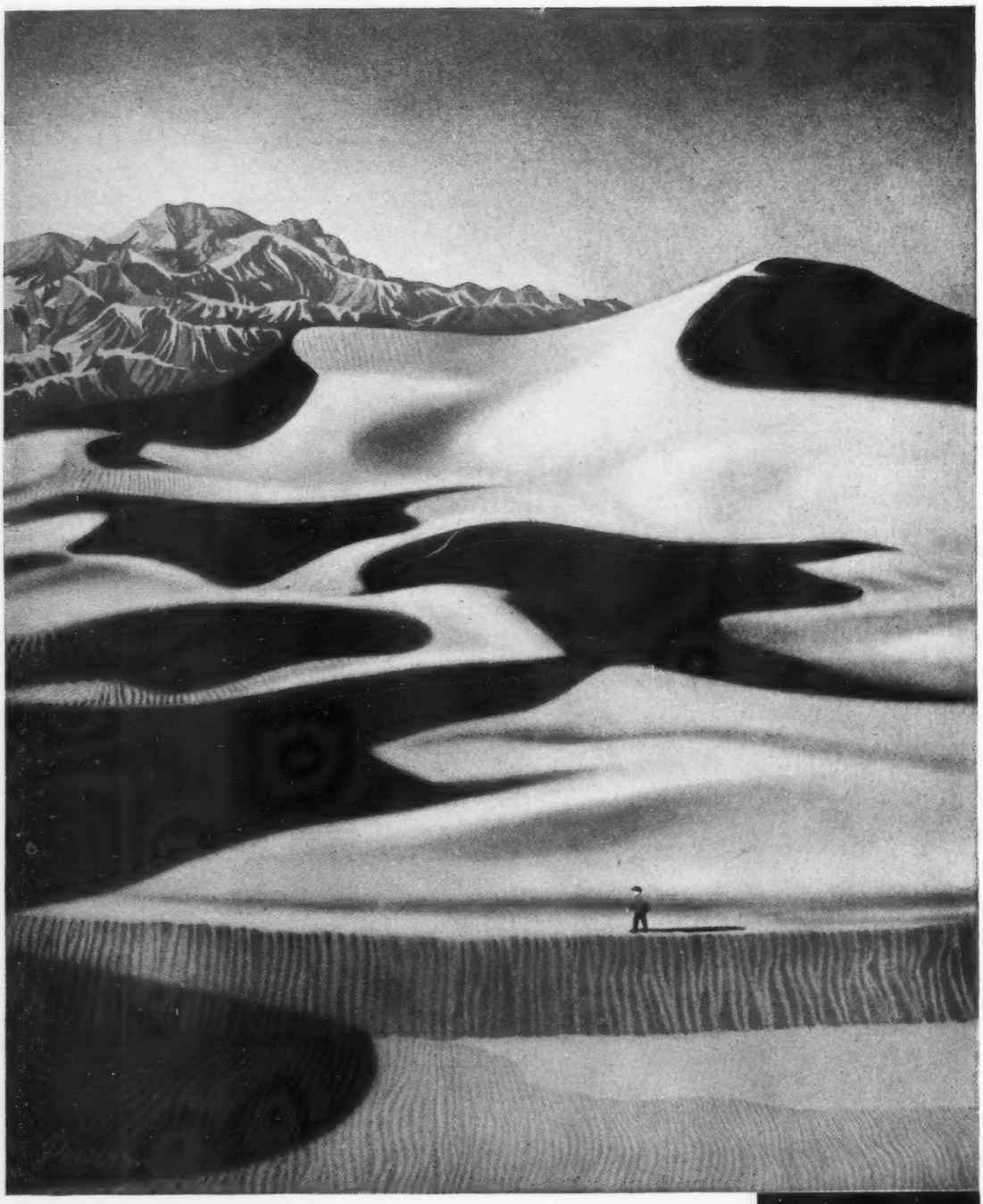

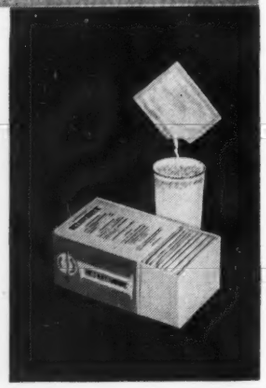

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References: 1. Carlson, A. J., in Stieglitz, E. J.: Geriatric Medicine, ed. 3, Philadelphia, J. B. Lippincott Company, 1954, p. 71. • 2. Dixon, H. H.; Peterson, R. D.; Dickel, H. A.; Jones, C. H., and West, E. S.: West J. Surg. *60*:327 (July) 1952.

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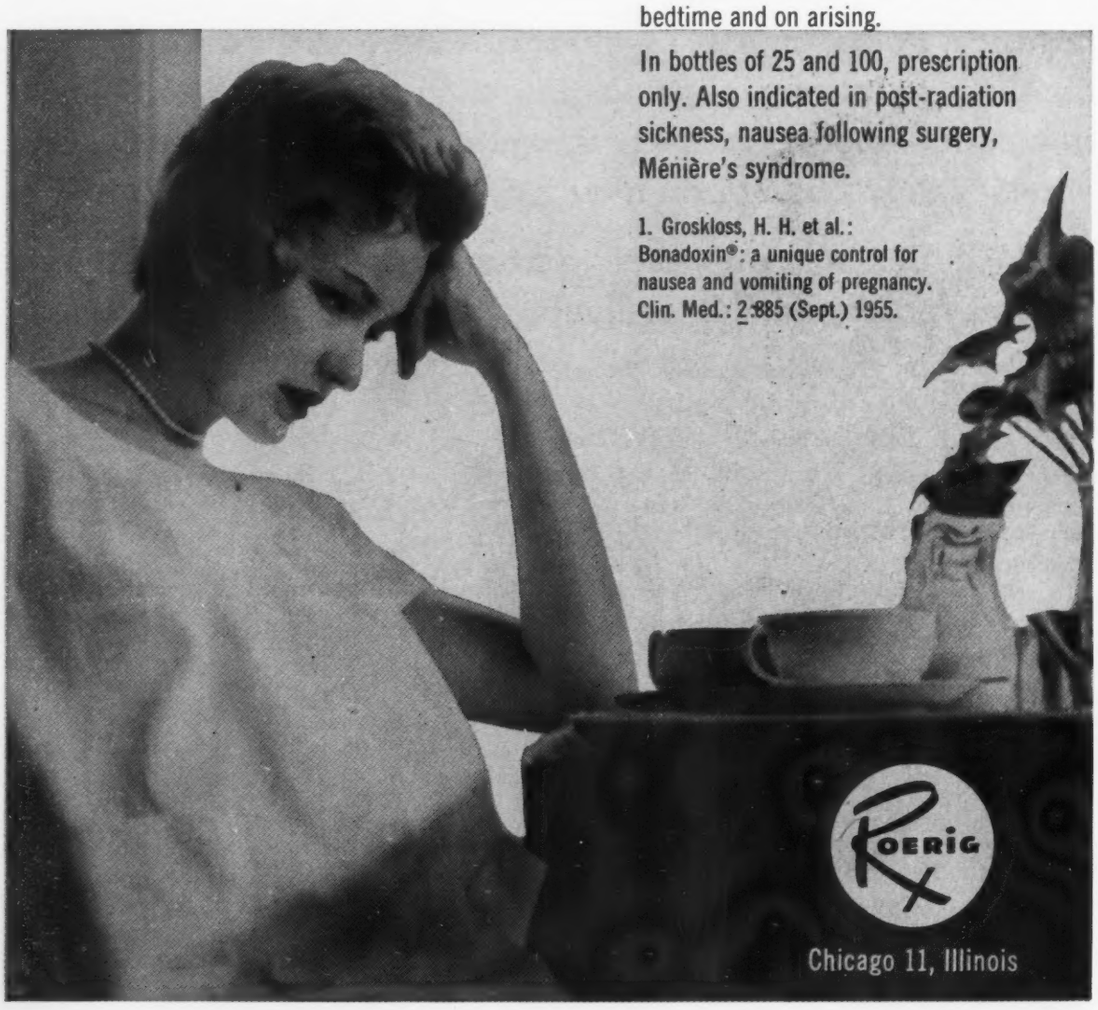

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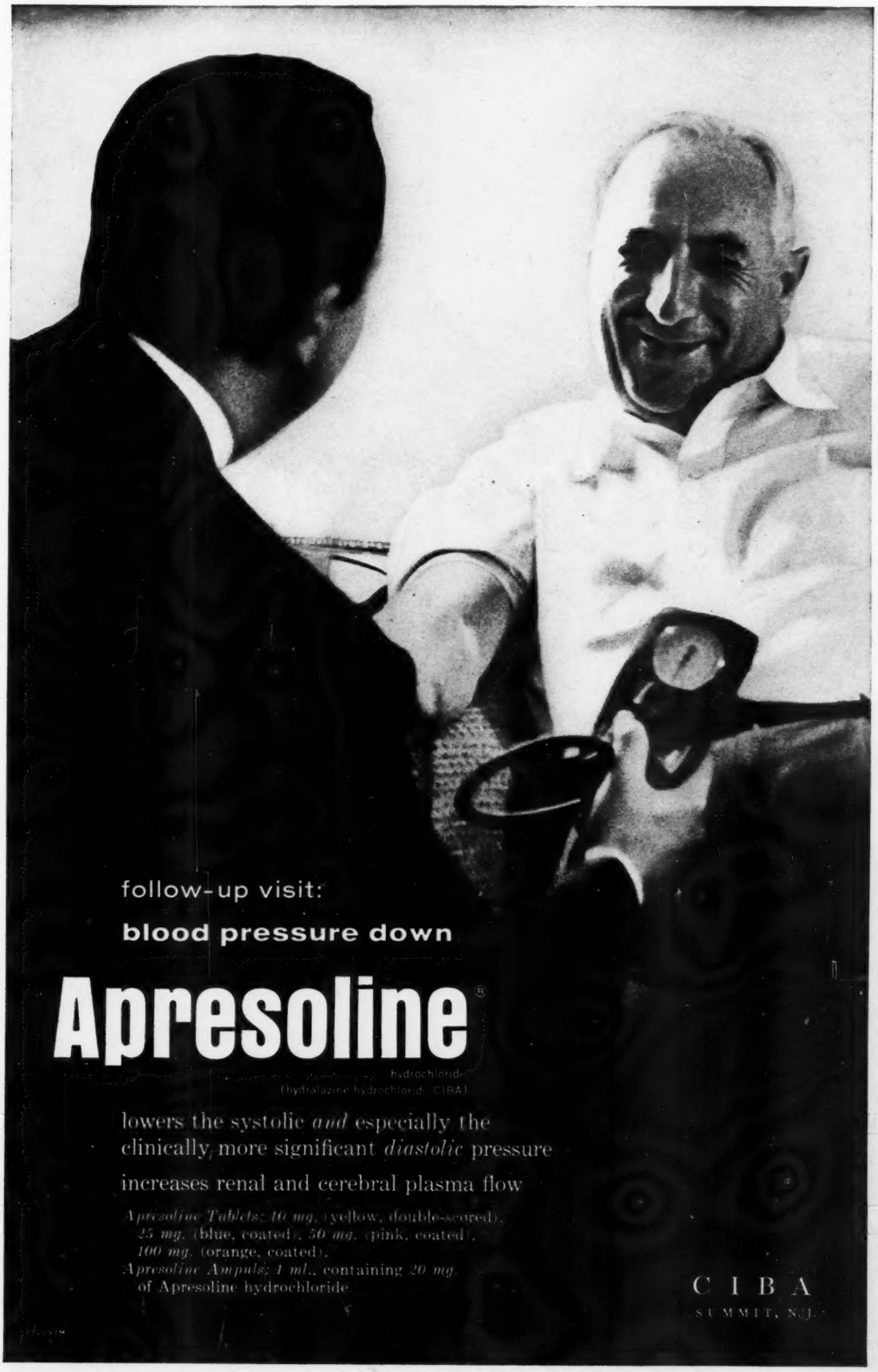
1. Groskloss, H. H. et al.: Bonadoxin®: a unique control for nausea and vomiting of pregnancy. Clin. Med.: 2:885 (Sept.) 1955.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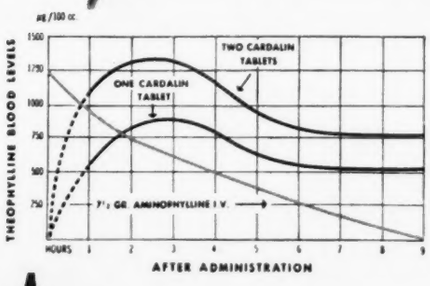

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To serve your patients today—Call your pharmacist for any additional product information you may need to help you prescribe Cardalin.

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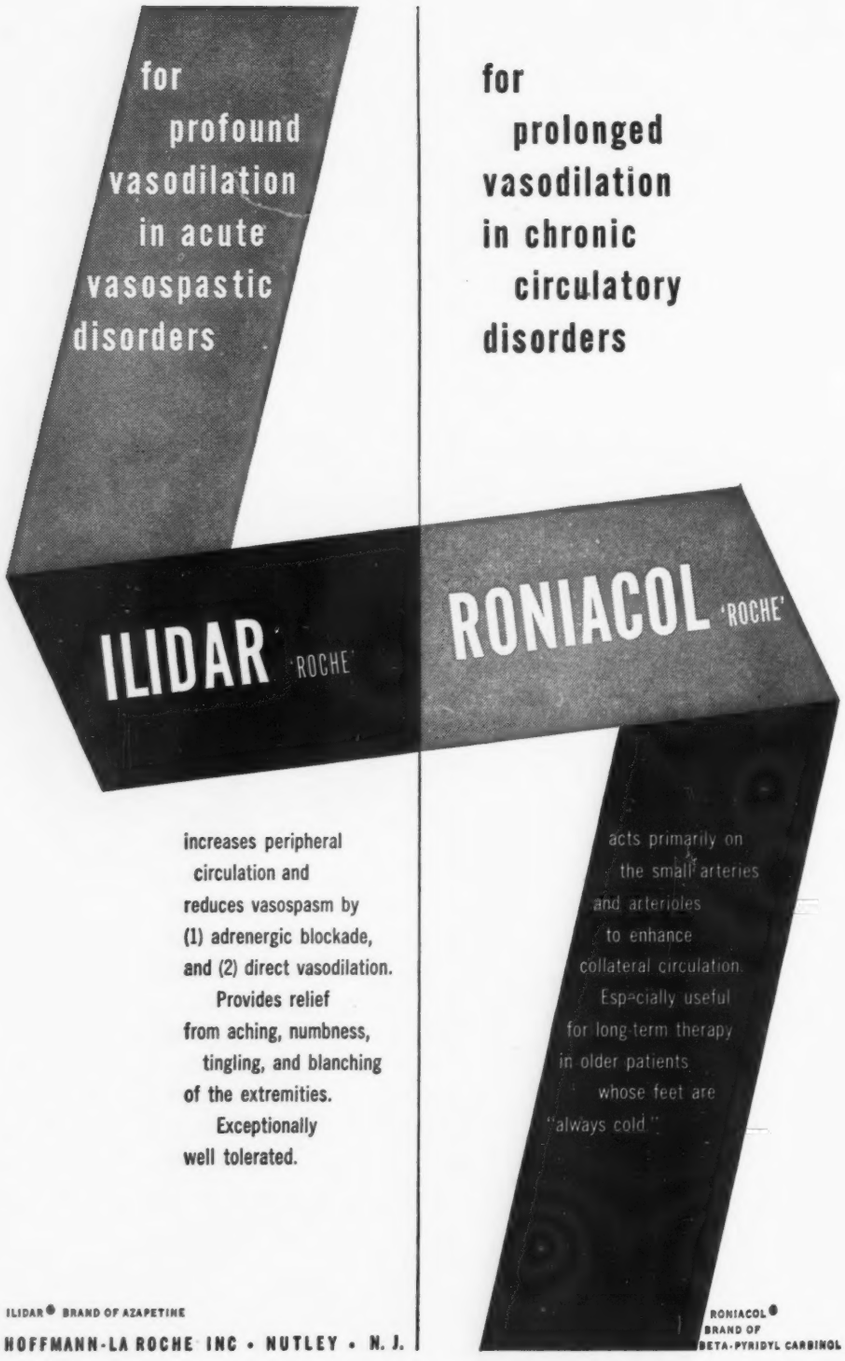

for profound vasodilation in acute vasospastic disorders
for prolonged vasodilation in chronic circulatory disorders
ILIDAR 'ROCHE'
RONIACOL 'ROCHE'
increases peripheral circulation and reduces vasospasm by (1) adrenergic blockade, and (2) direct vasodilation.
Provides relief from aching, numbness, tingling, and blanching of the extremities.
Exceptionally well tolerated.
acts primarily on the small arteries and arterioles to enhance collateral circulation.
Especially useful for long-term therapy in older patients whose feet are "always cold."
ILIDAR® BRAND OF AZAPETINE
RONIACOL® BRAND OF BETA-PYRIDYL CARBINOL
HOFFMANN-LA ROCHE INC • NUTLEY • N. J.

when
prescribing the
water-soluble
vitamin factors

KAPSEALS® COMBEX with VITAMIN C

Dependable dosage in convenient Kapseals makes COMBEX WITH VITAMIN C KAPSEALS a desirable prescription for combating frequently coexisting deficiencies of vitamin B-complex factors and of vitamin C.

and others of the COMBEX® family to meet a variety of needs for B factors

COMBEX KAPSEALS
COMBEX PARENTERAL } B-complex factors

THERA-COMBEX® KAPSEALS—High-potency B factors and C

TAKA-COMBEX® KAPSEALS—B factors, C, and starch digestant Taka-Diastase®

TAKA-COMBEX ELIXIR—B factors and Taka-Diastase

MEDICAMENTA VERA · PD Co. ·

PARKE, DAVIS & COMPANY, DETROIT, MICHIGAN

50008

when they can't stop coughing...

and won't stay home

Benylin Expectorant

When public embarrassment adds to the annoyance of a persistent cough, your patients will be grateful for BENYLIN EXPECTORANT. Corrective rather than suppressive in action, BENYLIN EXPECTORANT provides selected demulcent and expectorant agents, plus the potent antihistaminic-antispasmodic Benadryl® hydrochloride. Rapidly reducing frequency and severity of cough occurring with colds or allergic disorders, BENYLIN EXPECTORANT soothes irritated respiratory mucosa, makes cough looser and more productive, relaxes bronchial spasm, and relieves nasal stuffiness, sneezing, and lacrimation.

BENYLIN EXPECTORANT contains no narcotics... and does not depress the respiratory center. Its pleasant raspberry flavor appeals to patients of all ages.

BENYLIN EXPECTORANT contains in each fluid-ounce Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis) . . . . . 80 mg.
Ammonium chloride . . . . . 12 gr.
Sodium citrate . . . . . 5 gr.
Chloroform . . . . . 2 gr.
Menthol . . . . . 1/10 gr.
Alcohol 5%

DOSAGE: Adults, 1 or 2 teaspoonfuls every three to four hours. Children, ½ to 1 teaspoonful every four hours. Supplied in 16-ounce and 1-gallon bottles.

Available on prescription only.

50002

PARKE, DAVIS & COMPANY · DETROIT, MICHIGAN

unique combination

of two outstanding antihistaminics

AMBENYL® EXPECTORANT

for coughs due to colds or allergies

AMBENYL EXPECTORANT combines the two noted antihistaminics Benadryl® and Ambodryl® with other valuable agents to control cough through antispasmodic, antiallergic, decongestant, and demulcent actions.

Each fluidounce of pleasant-tasting AMBENYL EXPECTORANT contains:

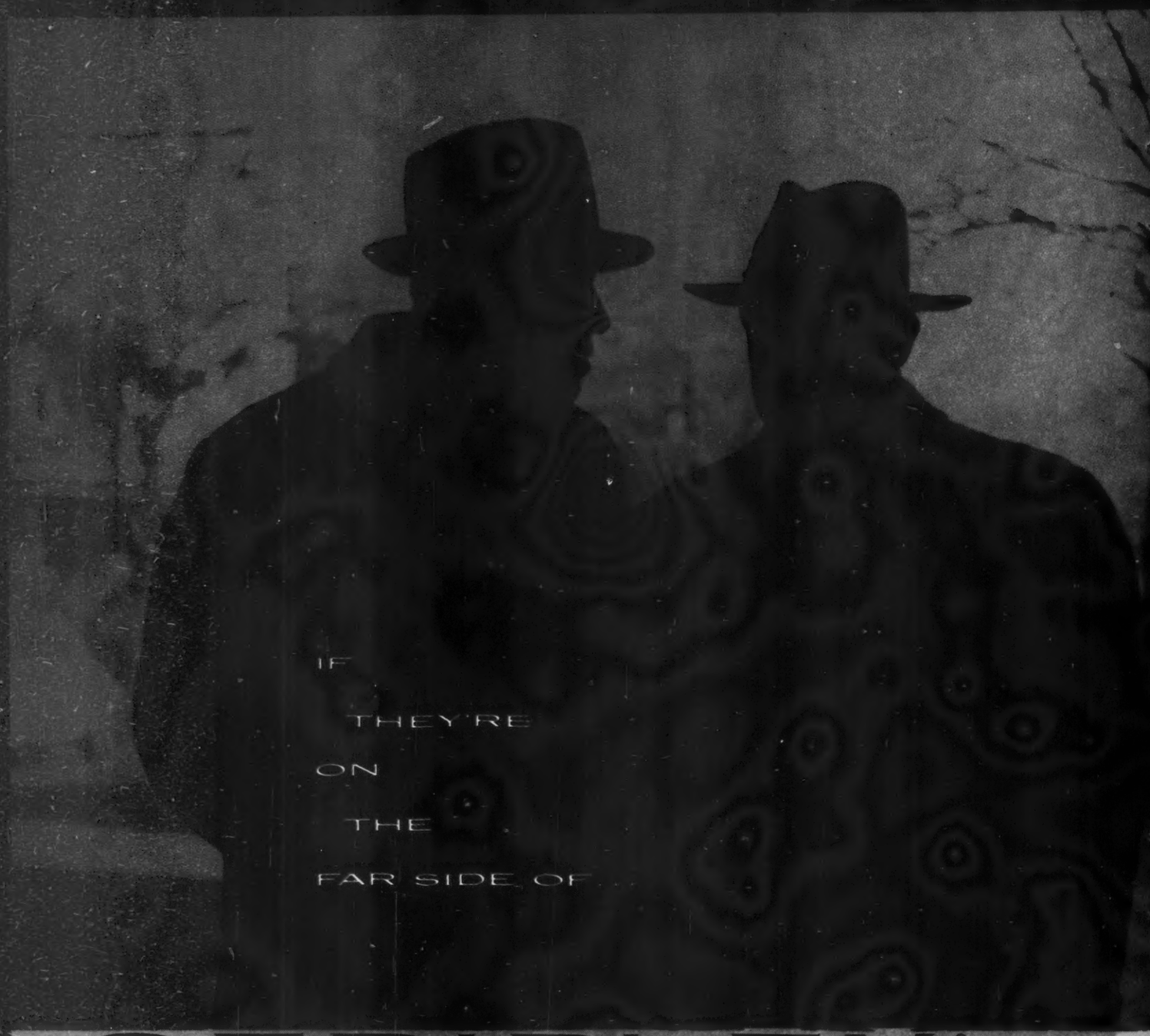
Ambodryl hydrochloride (bromodiphenhydramine hydrochloride, Parke-Davis)	24 mg.
Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	56 mg.
Dihydrocodeinone bitartrate	1/6 gr.
Ammonium chloride	8 gr.
Potassium guaiacolsulfonate	8 gr.
Menthol	q.s.
Alcohol	5%

Supplied in 16-ounce and 1-gallon bottles.

DOSAGE: Every three or four hours—adults, 1 to 2 teaspoonfuls; children, ½ to 1 teaspoonful.

PARKE, DAVIS & COMPANY · DETROIT, MICHIGAN

MEDICAMENTA VERA



GERIPLEX®

KAPSEALS®

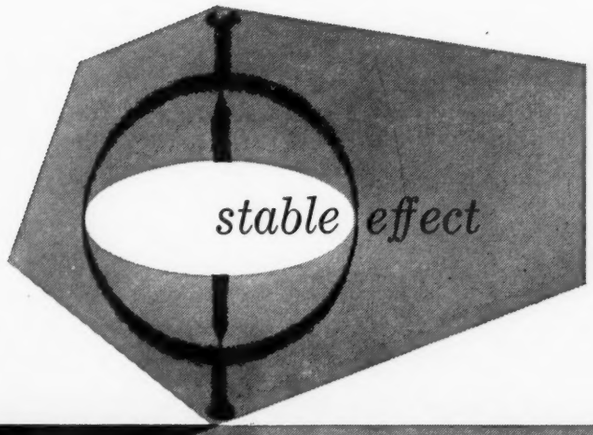
geriatric vitamin-mineral combination

• to supplement the regular dietary • in febrile illnesses • preoperatively or postoperatively • whenever the possibility of vitamin-mineral deficiency is increased

Each GERIPLEX Kapseal contains valuable mineral nutrients, eight important vitamins, the starch-digestant Taka-Diastase,® and rutin. Supplied in bottles of 100 and 500.

PARKE, DAVIS & COMPANY

DETROIT, MICHIGAN



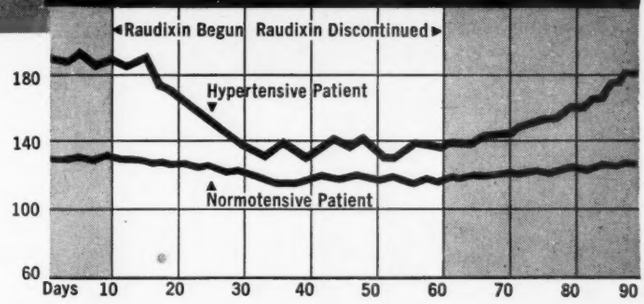
RAUDIXIN

SQUIBB WHOLE ROOT RAUWOLFIA SERPENTINA

in anxiety and tension states . . .
stable ataractic (tranquilizing) effect
without excessive sedation

in hypertension . . .
stable hypotensive effect without rapid peaks and declines in blood pressure

Comparative effect of Raudixin on the blood pressure of hypertensive patient and normotensive patient.



The hypotensive action of Raudixin is selective for the hypertensive state. For this reason, Raudixin does not significantly affect the blood pressure of normotensive patients.

DOSAGE: 100 mg. b.i.d. initially; may be adjusted within a range of 50 mg. to 500 mg. daily. Most patients can be adequately maintained on 100 mg. to 200 mg. daily.

SUPPLY: 50 mg. and 100 mg. tablets, bottles of 100, 1000 and 5000.

SQUIBB

'RAUDIXIN'® IS A SQUIBB TRADEMARK

Each SUR-BEX with C tablet contains:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} *(as cobalamin concentrate)*	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Liver Fraction 2, N. F.	300 mg. (5 grs.)
Brewer's Yeast, Dried	150 mg. (2½ grs.)

As a dietary supplement: 1 or 2 tablets daily.
For stress, or postoperative convalescence: 2 or more tablets daily.

603149

Abbott

Romilar — a real cough specific

A 10-mg dose of Romilar equals a 15-mg dose of codeine in specific antitussive effect. Yet Romilar® 'Roche' is non-narcotic; it does not cause drowsiness, nausea or constipation. Tablets, 10 mg; syrup, 10 mg/4 cc; expectorant, 15 mg Romilar plus 90 mg ammonium chloride per 5 cc.

ROCHE
Original Research
in Medicine and Chemistry

Gantricillin is Gantrisin plus penicillin in a single tablet. For severe infections, Gantricillin-300; for mild infections, Gantricillin (100); for pediatric infections, Gantricillin (acetyl)-200 suspension.

Gantricillin® Gantrisin® - brand of sulfisoxazole

original research in medicine and chemistry

a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried .	0.12 Gm.
Calcium ascorbate	60 mg.
(equivalent to 50 mg. ascorbic acid)	
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

BRISTOL, TENNESSEE
NEW YORK
KANSAS CITY
SAN FRANCISCO

The S. E. Massengill company

introducin

a new stance

flexin*

the first orally ective lissive†

dosage: Adults—1 to 2 t times a day with food or immediately —1 tablet two to four times a day.

supplied: Yellow, sc ttles of 50.

†**lissive:** Spasmolysis t interference with normal function

*T.M.

00286

true spasmolysis of skeletal muscle in musculoskeletal and neurological disorders effective up to 6 hours

Synthesized and characterized by McNeil Laboratories, FLEXIN is the first skeletal muscle relaxant *truly effective by mouth*. Its lissive action relieves the disability and pain of skeletal muscle spasm—common denominator of many musculoskeletal and neurological disorders.

not a mephenesin derivative

FLEXIN provides superior and long lasting—up to 6 hours—spasmolysis of voluntary muscle in low back syndromes, fibrositis, strains, sprains, and in noninflammatory rheumatic and arthritic disorders.

Striking results are reported in cerebral palsy. Over 65 per cent of spastics obtained definite reduction of excessive muscle tone. In addition, a highly significant number of patients with multiple sclerosis, spinal spasticity and Parkinsonism were benefited.

McNeil Laboratories, Inc., Philadelphia 32, Pa.

McNEIL

Erythromycin in treatment of pyoderma*

8/12/55

DISCHARGE SUMMARY

Patient, white female, age 39, entered hospital with a diagnosis of lymphoma, proved to be lymphosarcoma by biopsy.

Initially she was treated by X-ray radiation, adrenal cortical hormone and an antinauseant. During this regimen she developed a generalized rash which became infected. This was a drug reaction with infection due either to (1) scratching or (2) a low WBC count due to radiation. A number of boil-like lesions appeared over the body.

On 8/4 penicillin was started in a dosage of 600,000 units daily. Penicillin was continued for six days during which time the pyoderma became worse.

Aspirated material from the lesions yielded hem. S. aureus, coag. + and the following sensitivities were obtained: penicillin, more than 10 units; erythromycin, 10 mcg.; tetracycline, 50 mcg. When these results became available penicillin was discontinued.

On 8/9, erythromycin was started in a dosage of 200 mgm. q.i.d. Marked improvement was noted very soon and by 8/12 almost complete healing of all lesions had occurred. Patient was afebrile throughout.

Final Diagnosis: (1) lymphosarcoma (2) secondary pyoderma due to hemolytic Staphylococcus aureus.

Result: complete healing of secondary pyoderma with erythromycin.

*Communication to Abbott Laboratories

specific against coccic infections

Now, you can prescribe an antibiotic (*Filmtab* ERYTHROCIN) that provides *specific therapy* against staph-, strep- or pneumococci. Since these organisms cause most bacterial respiratory infections (and since they are the very organisms most sensitive to ERYTHROCIN) doesn't it make good sense to prescribe ERYTHROCIN when the infection is coccic?

filmtab®

Erythrocin®
(Erythromycin, Abbott)
STEARATE

with little risk of serious side effects

Since ERYTHROCIN is inactive against gram-negative organisms, it is less likely to alter intestinal flora—with an accompanying low incidence of side effects. Also, your patients seldom get the allergic reactions sometimes seen with penicillin. Or loss of accessory vitamins during ERYTHROCIN therapy. *Filmtab* ERYTHROCIN (100 and 250 mg.), bottles of 25 and 100. Abbott

filmtab®

Erythrocin®
(Erythromycin, Abbott)
STEARATE

®Filmtab—Film sealed tablets; patent applied for

601105

Throughout the world...

use in millions of cases and reports by thousands of physicians have built confidence in TERRAMYCIN®

BRAND OF OXYTETRACYCLINE

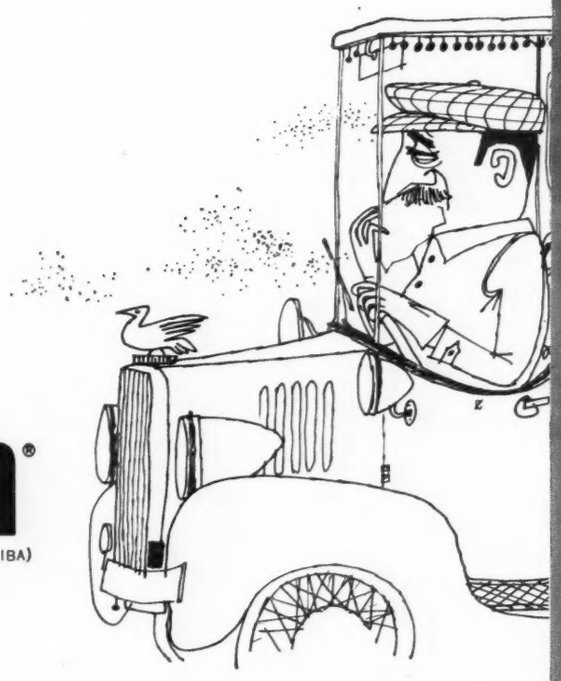
...well-tolerated, rapidly effective broad-spectrum antibiotic of choice.

Capsules, tablets, taste-tempting liquid forms and special preparations for parenteral, topical and ophthalmic use.

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

because
your allergic patients
need a lift
a new R_x...



Plimasin®

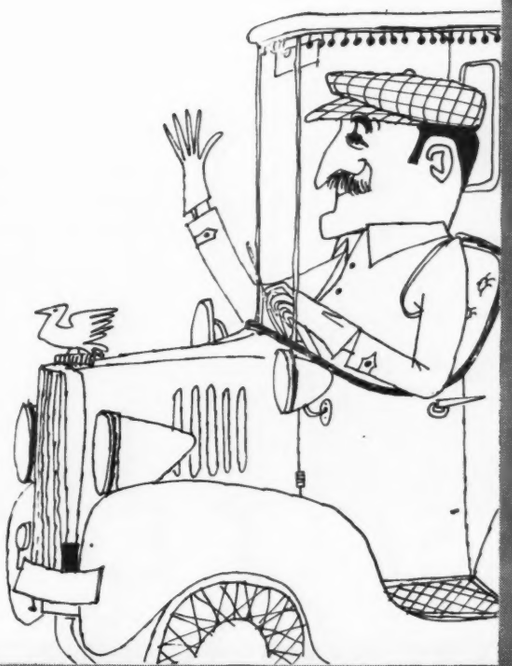
(tripelennamine hydrochloride and methyl-phenidylacetate CIBA)

new, mild stimulant
and antihistamine

boost their spirits... relieve their allergic symptoms

So often the allergic patient is tired, irritable, depressed—mentally and physically debilitated. Frequently, antihistaminic agents themselves are sedative, adding to this already fatigued and disconsolate state.

Plimasin, because it combines a proved antihistamine with a new, mild psychomotor stimulant, overcomes depression and fatigue while it achieves *potent* antiallergic effects. Its new stimulant component—Ritalin—is totally different from amphetamine: smoother, gentler in action, devoid of pressor effect.



DOSAGE: *One or 2 tablets as required.*

Each Plimasin tablet contains 25 mg. Pyribenzamine® hydrochloride (tripelennamine hydrochloride CIBA) and 5.0 mg. Ritalin® (methyl-phenidylacetate CIBA).

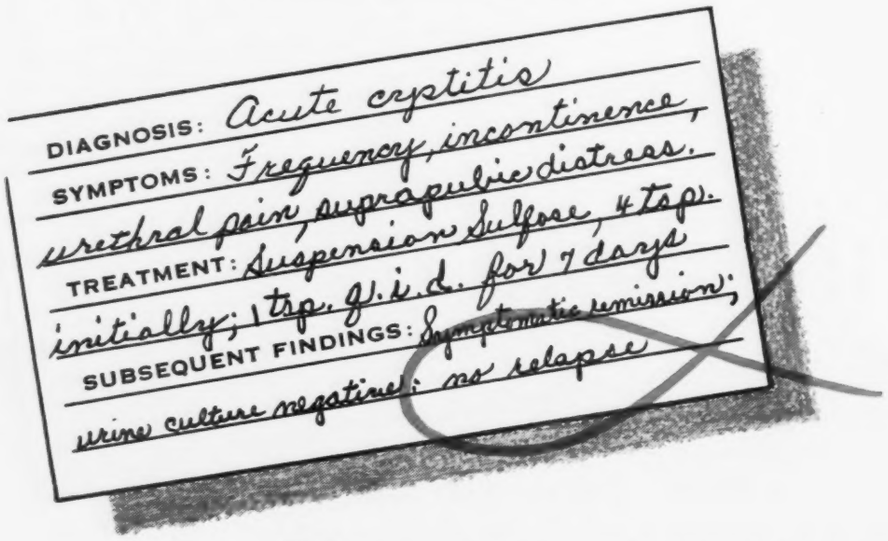
CIBA SUMMIT, N. J.

2/2191M

In Urinary-Tract Infection . . .

the *Test* of Effective Therapy

". . . there were no relapses in those freed of the initial urinary infection. . . ."[1]


DIAGNOSIS: Acute cystitis
SYMPTOMS: Frequency, incontinence, urethral pain, suprapubic distress.
TREATMENT: Suspension Sulfose, 4 tsp. initially; 1 tsp. q.i.d. for 7 days
SUBSEQUENT FINDINGS: Symptomatic remission; urine culture negative; no relapse

Post-treatment recurrence is common in urinary-tract infection.

With Suspension SULFOSE, however, Bohne and Chase[1] report no recurrence: ". . . no patient returned for additional treatment . . . 79% were freed of urinary infection . . ." Infection *controlled*, relapse *prevented*—this is the test of effective therapy.

Suspension SULFOSE offers the advantages of three potentiating sulfonamides in an *alumina-gel base*. Supported by comparative studies, it is a combination for higher and more prolonged blood levels[2] and maximal renal safety.[2,3]

Supplied: Suspension SULFOSE, bottles of 1 pint. Also available, Tablets SULFOSE, bottles of 100 and 1000. Each 5-cc. teaspoonful and tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine, and sulfamethazine.

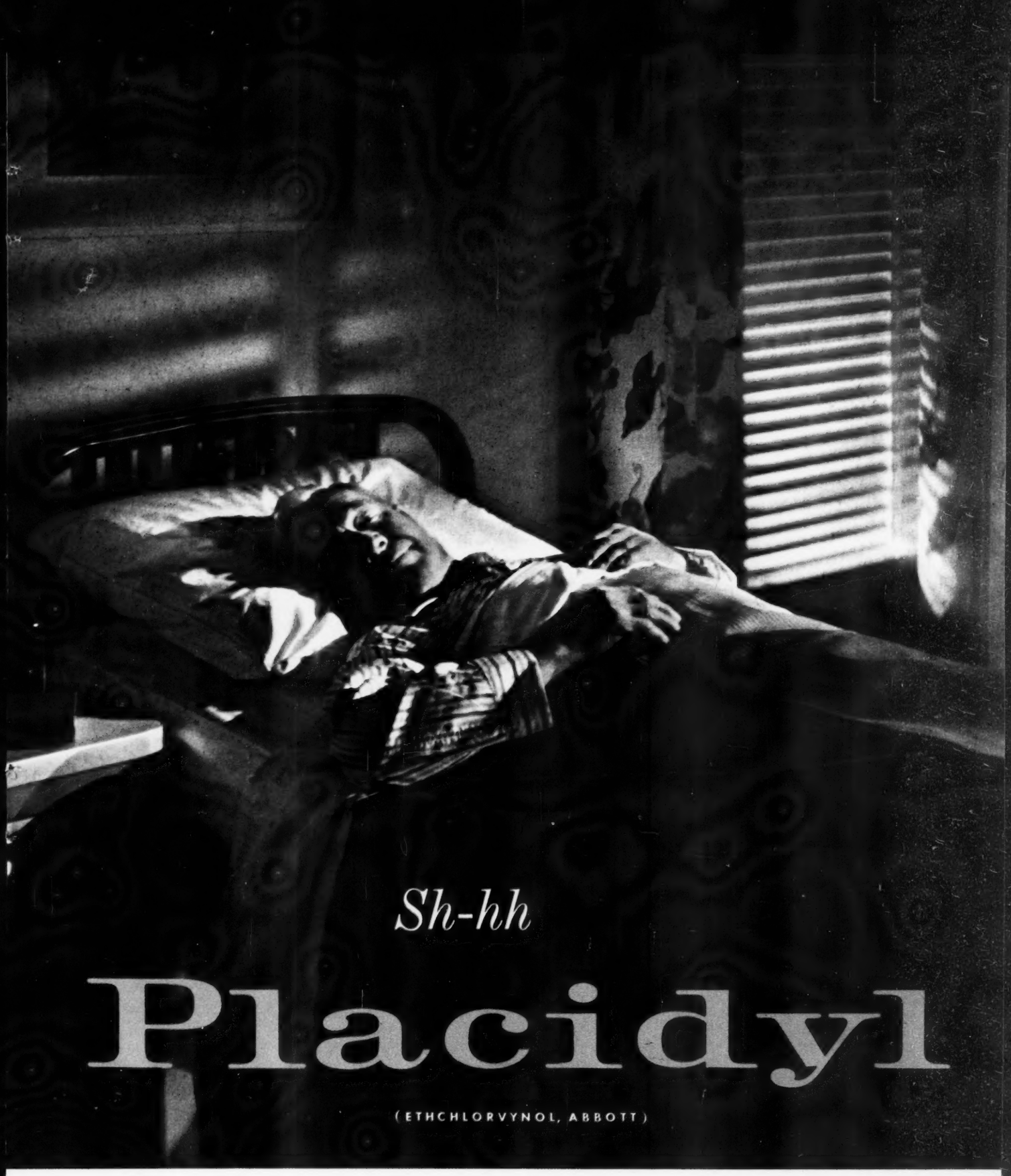
1. Bohne, A.W., and Chase, W.E.: Am. J.M.Sc. March, 1956. 2. Berkowitz, D.: Antibiot. & Chemo. *3*:618 (June) 1953. 3. Editorial: J.A.M.A. *159*:1459 (Dec. 10) 1955.

Wyeth®
Philadelphia 1, Pa.

suspension

SULFOSE®

Triple Sulfonamides (Sulfadiazine, Sulfamerazine, Sulfamethazine)



Sh-hh

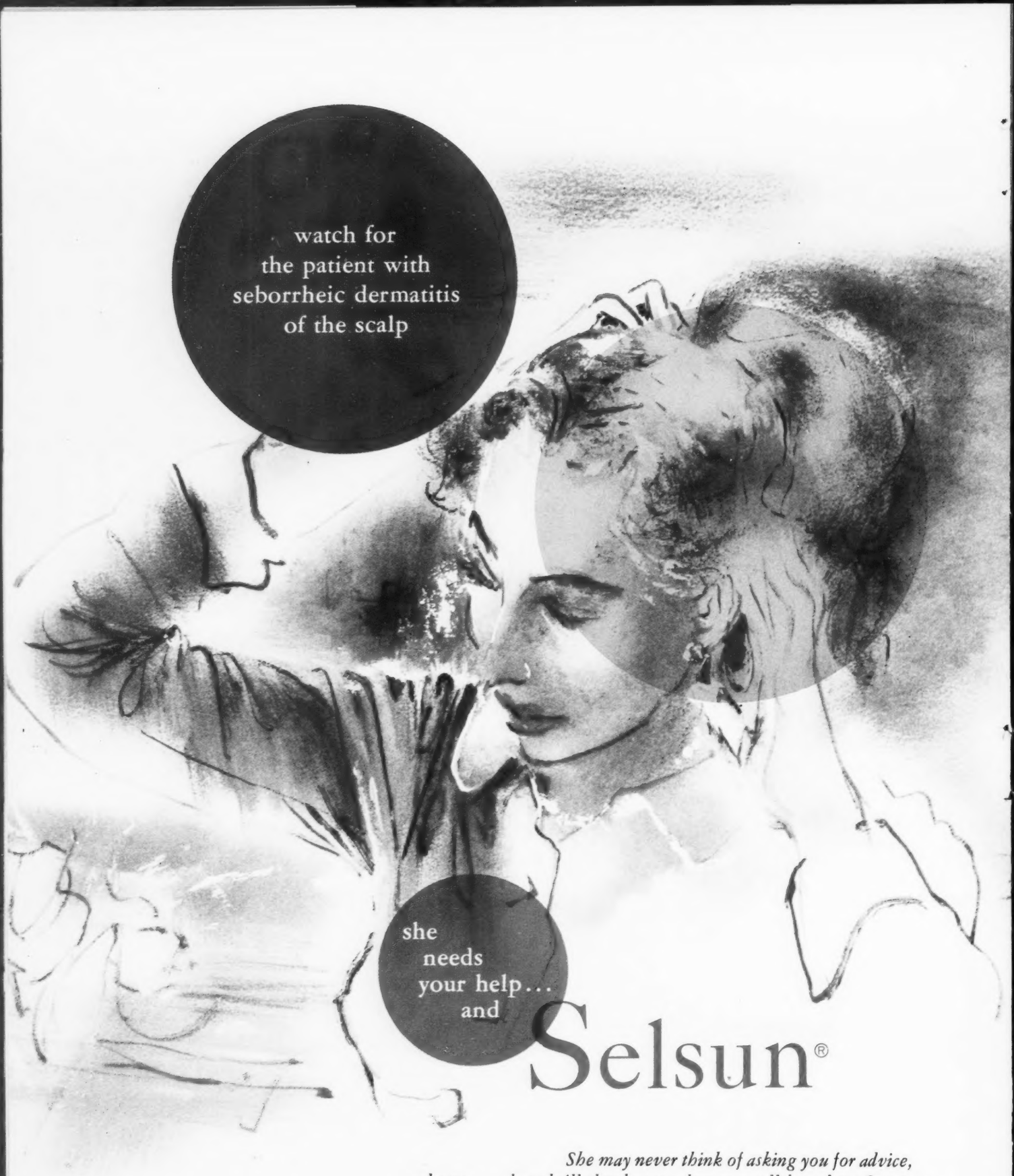
Placidyl

(ETHCHLORVYNOL, ABBOTT)

nudges your patient to sleep

Gentle as a lullaby, this new nonbarbiturate hypnotic brings tranquil sleep, and is useful even for those patients with liver or kidney disease. 500 mg. capsules, bottles of 100.

Abbott



Selsun®

She may never think of asking you for advice, doctor . . . but she'll thank you when you tell her about SELSUN. *Your prescription for* SELSUN (and SELSUN is sold only on prescription) *will give her lasting relief from the symptoms of seborrheic dermatitis of the scalp or dandruff . . . quickly, easily, economically. Simple and pleasant to use.* SELSUN *is applied and rinsed out while washing the hair, takes little time. Completely controls 81-87% of seborrheic dermatitis, 92-95% of dandruff cases. In 4-fluidounce bottles with directions.* Abbott

®Selenium Sulfide, Abbott

for balance in cardiac control

DIGOXIN 'B.W.&CO.'®

a conveniently administered dosage form for every need

for simplified emergency digitalization:

'WELLCOME'® brand DIGOXIN INJECTION
0.5 mg. in 2 cc.

may be given intramuscularly, as well as intravenously, without dilution
Boxes of 12 and 100 ampuls

for dependable maintenance:

'TABLOID'® brand DIGOXIN *0.25 mg.* *Scored (white)*
Bottles of 100 and 1,000 tablets

'TABLOID'® brand DIGOXIN *0.5 mg.* *Scored (green)*
Bottles of 100 and 1,000 tablets

for infants and children:

'WELLCOME'® brand DIGOXIN ELIXIR PEDIATRIC
0.05 mg. in each cc.

Supplied with a dropper calibrated to 1 cc. in graduations of 0.2 cc. (0.01 mg. Digoxin)
Bottles of 2 fluid ounces

BURROUGHS WELLCOME & CO. (U.S.A.) INC., *Tuckahoe, New York*

New suppositories eradicate urethral infection and pain

The suppository this patient inserted at home this morning keeps her comfortable all day and allows her to follow her normal routine

new—the only antimicrobial urethral suppository

fast—prompt relief of pain and burning

sure—the nitrofuran, FURACIN, eradicates most bacteria common to urethral infections

easy—patient inserts suppositories at home

safe—only rare irritation in over 340 reported cases*

proved—"the suppository method of medication has proved its worth"*

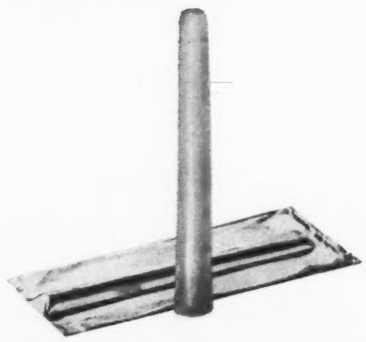
PRESCRIBE. for bacterial (granular) urethritis; for topical anesthesia and prophylaxis of infection before and after instrumentation

FORMULA: 0.2% FURACIN (brand of nitrofurazone) and 2% diperodon·HCl in a water-miscible base. Sealed in foil. Box of 12

to prevent cross-infection

Use the urethral suppositories with **FURACIN vaginal** Suppositories to prevent urethrovaginal cross-infection.

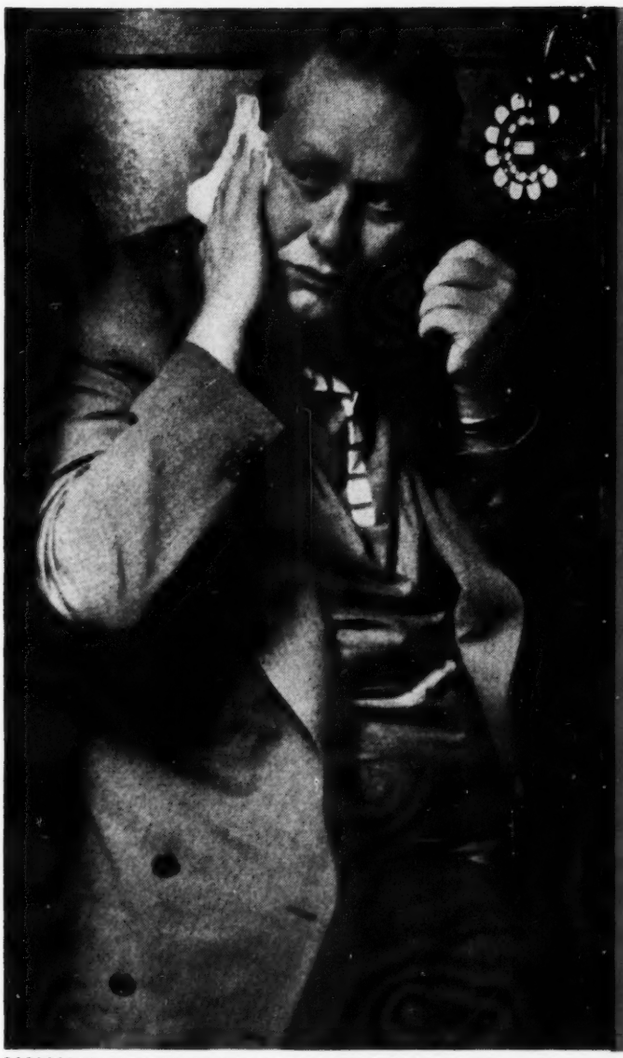
FORMULA: 0.2% FURACIN (brand of nitrofurazone) in a water-miscible base. Sealed in yellow foil. Box of 12.



FURACIN®
urethral
SUPPOSITORIES

*Youngblood, V. H.: J. Urol. 70:926, 1953.

EATON LABORATORIES, Norwich, N.Y. **NITROFURANS** a new class of antimicrobials neither antibiotics nor sulfas



It's not a distress call... not yet... but it could be— For effective appetite suppression in obesity...

AMBAR™ Robins

METHAMPHETAMINE AND PHENOBARBITAL

TABLETS AND EXTENTABS*

The "distress call" in obesity often comes from the emotional "misfit," unable to control mood or appetite. Ambar allays this hunger sensation by *gently* lifting the depressed mood, and *subtly* reducing the emotional distresses so often responsible for the urge to overeat. Ambar brings the obese patient's appetite "down to normal"...

...without peaks of stimulation
...without troughs of depression
...without significant cardiovascular effects
...without postmedication "jitters"

AMBAR™ TABLETS

Methamphetamine Hydrochloride . . 3.33 mg.
Phenobarbital (1/3 gr.) . . . . . 21.6 mg.

Average duration of therapeutic effects 4 hours

AMBAR™ EXTENTABS®

Methamphetamine Hydrochloride . . 10.0 mg.
Phenobarbital (1 gr.) . . . . . 64.8 mg.

Average duration of therapeutic effects 10-12 hours

•

Literature available on request.

*Robins' registered trade-mark for Extended Action tablets.

A. H. ROBINS COMPANY, INC., RICHMOND, VIRGINIA

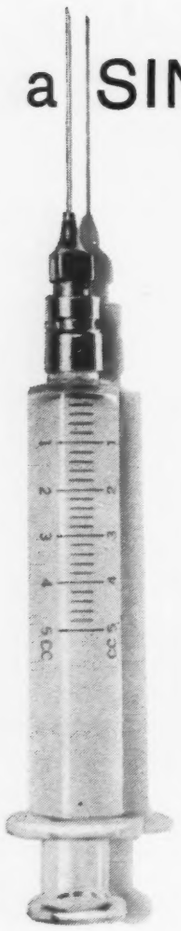
Ethical Pharmaceuticals of Merit Since 1878

treat adrenocortical insufficiency

without the
difficulties
of
implants

without the
unpleasantness
of daily
injections

with a SINGLE injection a month



Percorten®

trimethylacetate

(desoxycorticosterone trimethylacetate CIBA)

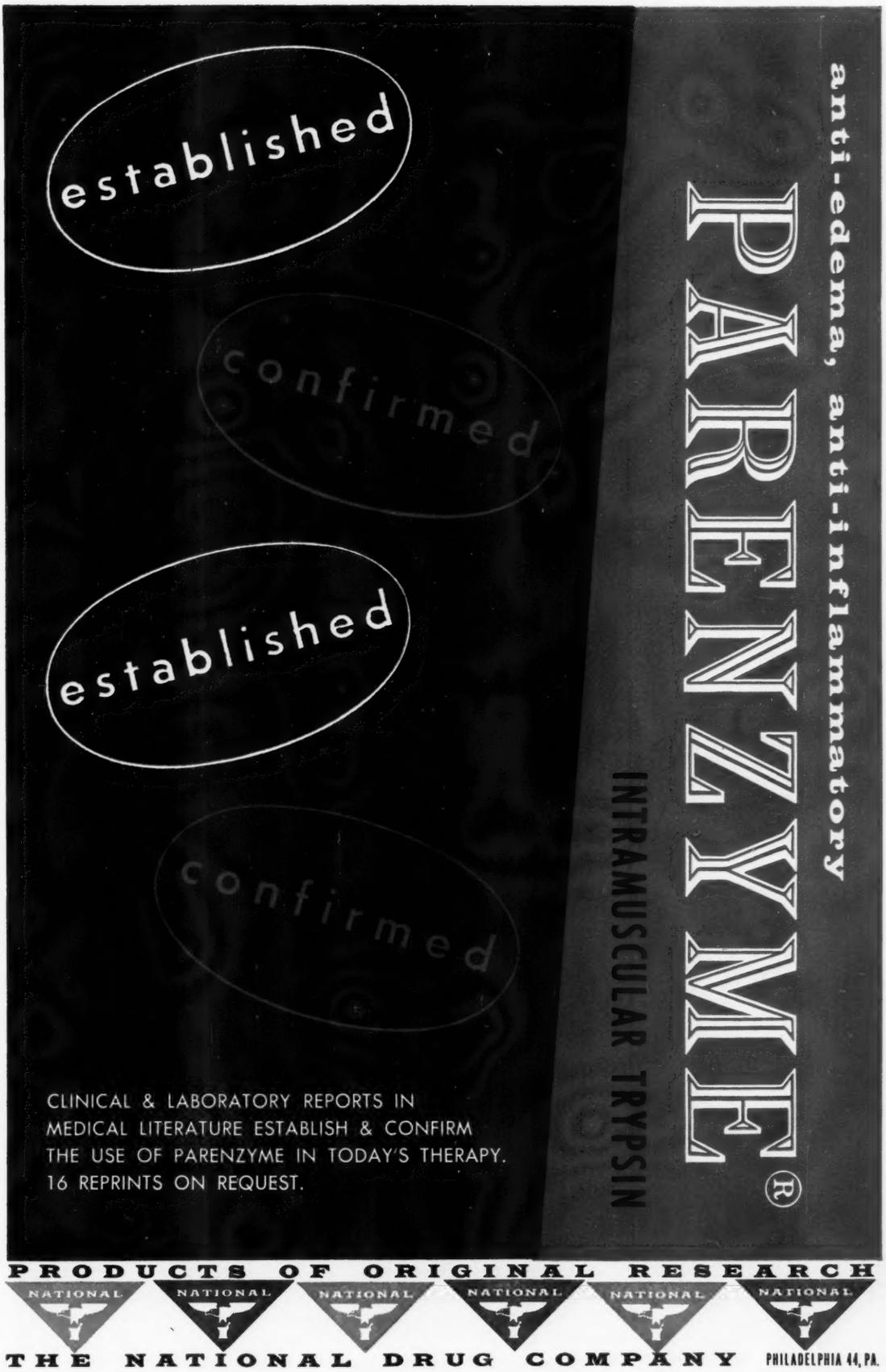
Percorten trimethylacetate, developed after more than 3 years of research by CIBA, provides expedient, lasting hormonal support for the patient with adrenocortical hypofunction . . . avoiding both the uncertainty of surgical implantation and the vexation of daily injections. With once-a-month therapy, a single injection will produce prolonged activity without acute signs of overdosage.[1]

Multiple-dose Vials, 4 ml., containing 25 mg. Percorten trimethylacetate per ml. as an aqueous microcrystalline suspension for intramuscular use only.

1. Frawley, T. F., and Forsham, P. H.: J. Clin. Endocrinol. *11*:772 (July) 1951.

CIBA
SUMMIT, N. J.

2/22334



PRODUCTS OF ORIGINAL RESEARCH

NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL

THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

Upjohn

Ulcer protection that lasts all night:

Pamine* BROMIDE

Tablets

Each tablet contains:
Methscopolamine bromide ..... 2.5 mg.

Average dosage (ulcer):
One tablet one-half hour before meals, and 1 to 2 tablets at bedtime.

Supplied: Bottles of 100 and 500 tablets

Syrup

Each 5 cc. (approx. 1 tsp.) contains:
Methscopolamine bromide ..... 1.25 mg.

Dosage:
1 to 2 teaspoonfuls three or four times daily.

Supplied: Bottles of 4 fluidounces

Sterile Solution

Each cc. contains:
Methscopolamine bromide ..... 1 mg.

Dosage:
0.25 to 1.0 mg. (¼ to 1 cc.), at intervals of 6 to 8 hours, subcutaneously or intramuscularly.

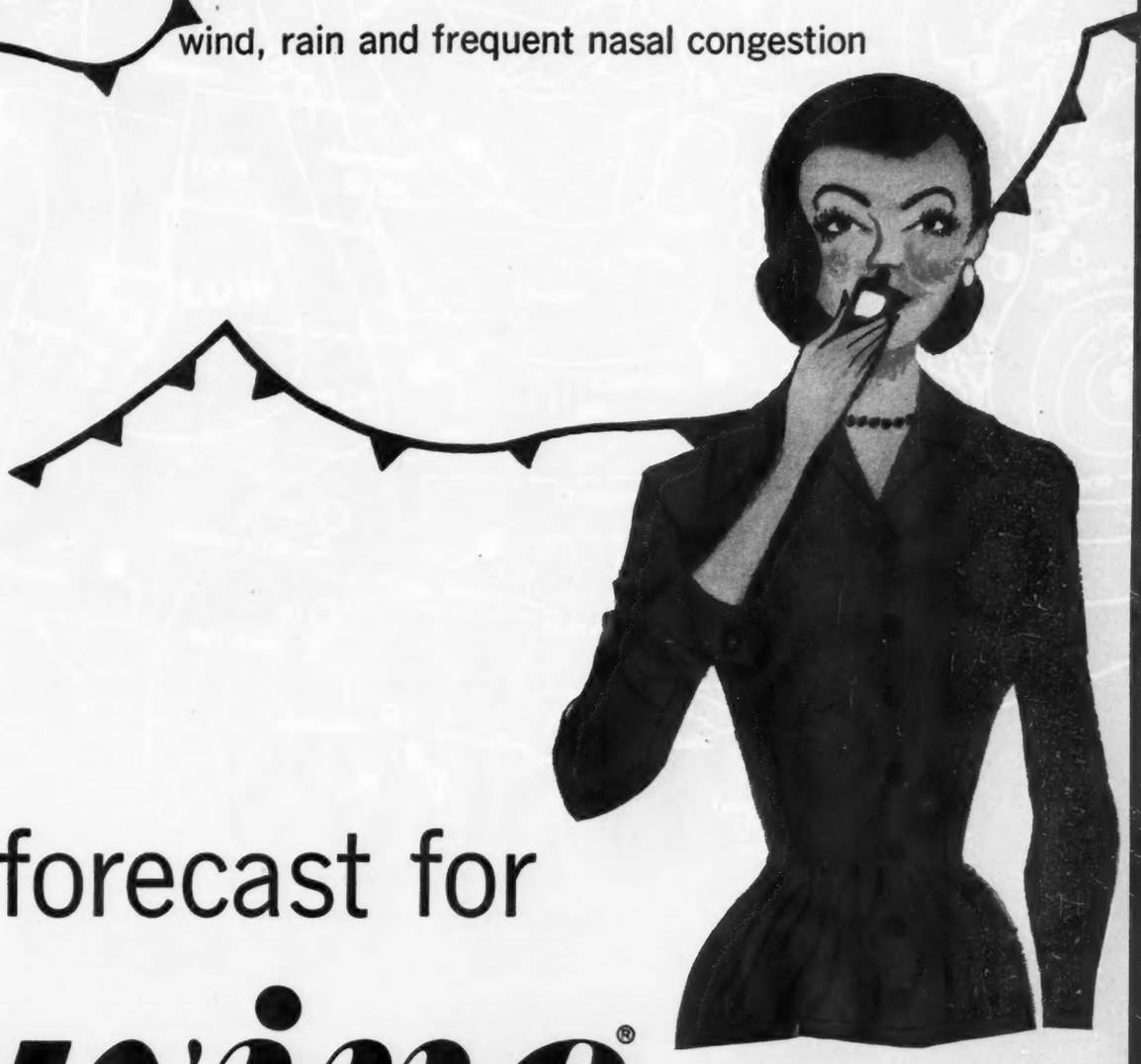
Supplied: Vials of 1 cc.

*TRADEMARK, REG. U. S. PAT. OFF.—THE UPJOHN BRAND OF METHSCOPOLAMINE

The Upjohn Company, Kalamazoo, Michigan

forecast:

wind, rain and frequent nasal congestion



a forecast for

Tyzine®

brand of tetrahydrozoline hydrochloride

a "superior"[1-3] nasal decongestant

providing nasal patency in minutes (almost immediately after instillation) for hours (up to 6 hours with a single dose) without rebound engorgement...

odorless, tasteless and free of sting, burn or irritation

"In addition ... [TYZINE] shortened the usual course of each infection, and, also either prevented or aborted complications..."[1]

supplied:

TYZINE Nasal Solution, in 1-oz. dropper bottles, 0.1%. TYZINE Nasal Spray, in plastic bottles, 15 cc., 0.1%. TYZINE Pediatric Nasal Drops, in 1/2-oz. bottles, 0.05%, with calibrated dropper for precise dosage.

1. Graves, J. W.: Eye, Ear, Nose & Throat Month. 34:670, 1955. 2. Menger, H. C.: New York J. Med. 55:812, 1955. 3. Neistadt, I.: A.M.A. Arch. Otolaryng. 62:143, 1955.

Pfizer

PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

When the stress of daily living becomes too great...

STRESSCAPS*

Stress Formula Vitamins Lederle

STRESSCAPS help restore efficiency by replacing depleted essential vitamins. This comprehensive supplement is based on the formula suggested by the National Research Council, with the addition of Vitamin K. *One capsule daily.*

Each Capsule Contains:

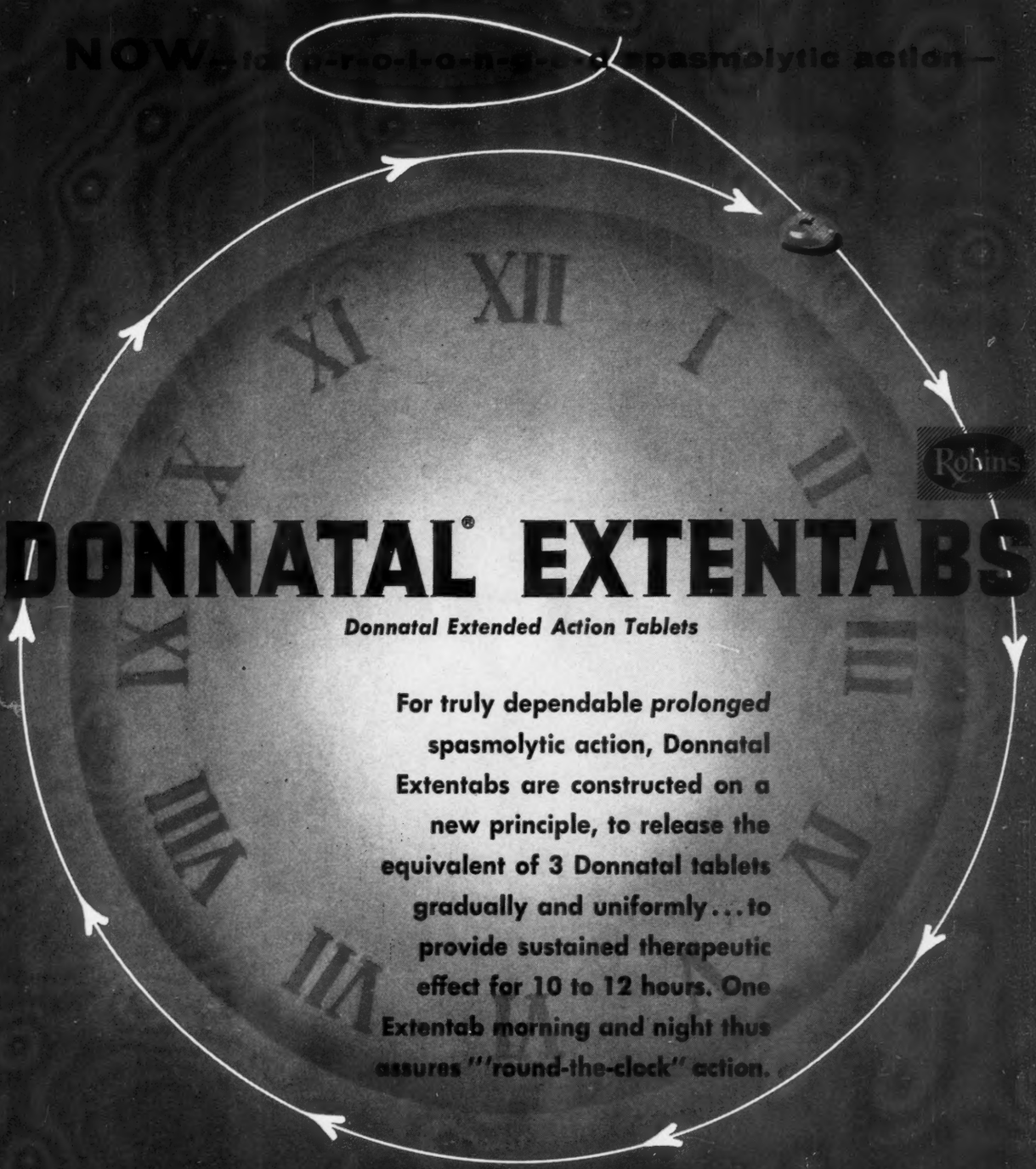
Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

LEDERLE LABORATORIES DIVISION *AMERICAN CYANAMID COMPANY* PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

Lederle

NOW—[illegible] spasmolytic action—



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DONNATAL® EXTENTABS

Donnatal Extended Action Tablets

For truly dependable *prolonged* spasmolytic action, Donnatal Extentabs are constructed on a new principle, to release the equivalent of 3 Donnatal tablets gradually and uniformly . . . to provide sustained therapeutic effect for 10 to 12 hours. One Extentab morning and night thus assures "'round-the-clock" action.

Each Donnatal Extentab contains:

Hyoscyamine Sulfate . .	0.3111 mg.
Atropine Sulfate	0.0582 mg.
Hyoscine Hydrobromide	0.0195 mg.
Phenobarbital (¼ gr.) . .	48.6 mg.

Also available — **DONNATAL:** tablets, capsules and elixir

A. H. ROBINS CO., INC. • RICHMOND 20, VA.

Ethical Pharmaceuticals of Merit since 1878

*Trade Mark

gentle

is the word

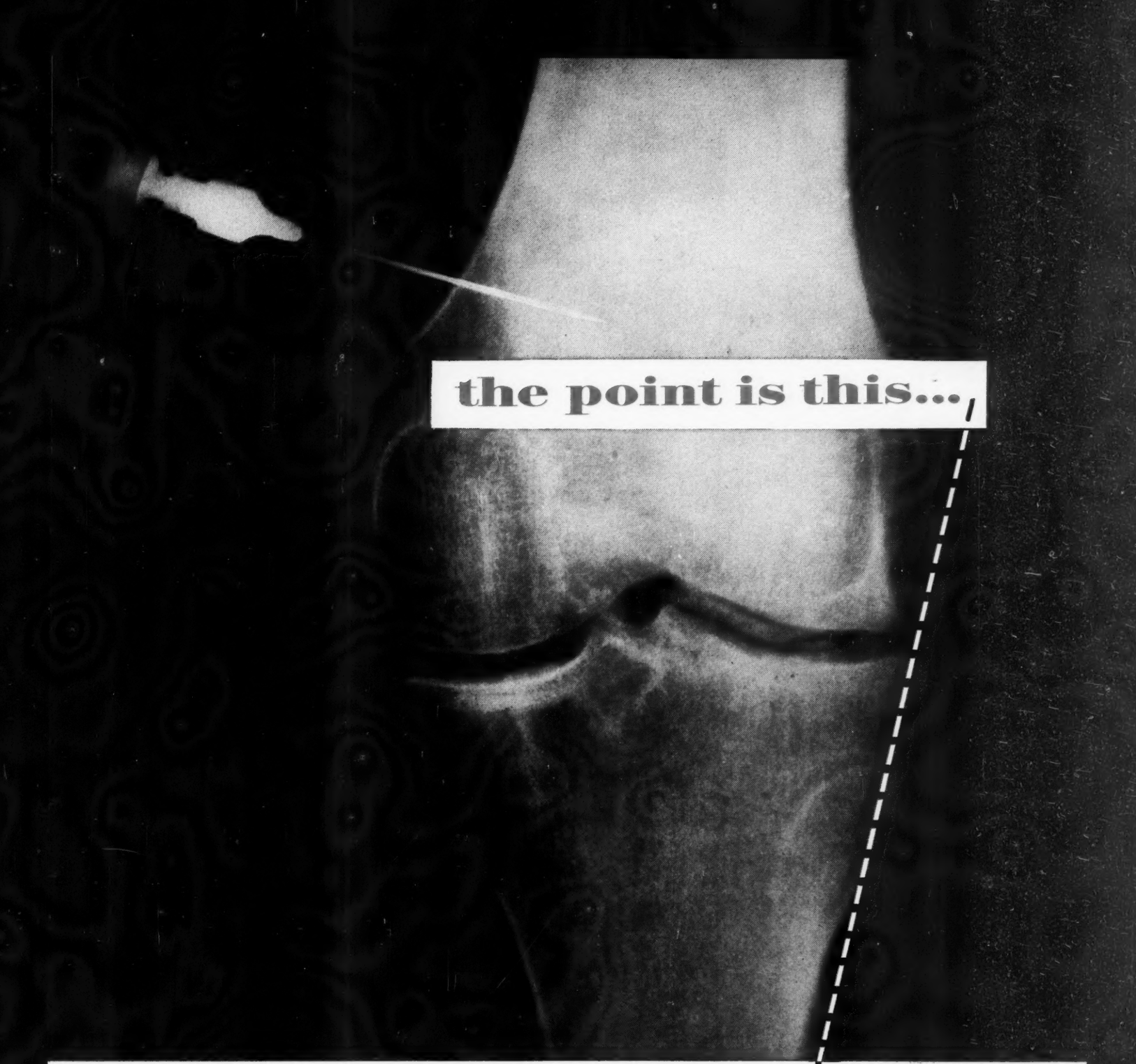
for Noludar

Mild, yet positive in action, Noludar 'Roche' is especially suited for the tense patient who needs to relax and remain clear-headed—or for the insomniac who wants a refreshing night's sleep without hangover. Not a barbiturate, not habit-forming. Tablets, 50 and 200 mg; elixir, 50 mg per teasp.

Noludar® brand of methyprylon
(3,3-diethyl-5-methyl-
2,4-piperidinedione)

ROCHE

Original Research in
Medicine and Chemistry



HydroCortone® -T B A

(HYDROCORTISONE TERTIARY-BUTYLACETATE, MERCK)

gives the arthritic patient more days of freedom from joint symptoms—in many patients the anti-rheumatic effect persists 2 to 10 times longer than after injection of hydrocortisone acetate. Its action is local and without systemic effect.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

SUPPLIED: SALINE SUSPENSION HYDROCORTONE-TBA—25 MG./CC., VIALS OF 5 CC.

the only broad spectrum antibiotic preparation that:

1 provides the antimicrobial activity of tetracycline

Because it contains Steclin (Squibb Tetracycline), the well tolerated broad spectrum antibiotic, MYSTECLIN is an effective therapeutic agent for many common infections. Most pathogenic bacteria, as well as certain large viruses, certain Rickettsiae, and certain protozoans, are susceptible to Mysteclin.

2 protects the patient against monilial superinfection

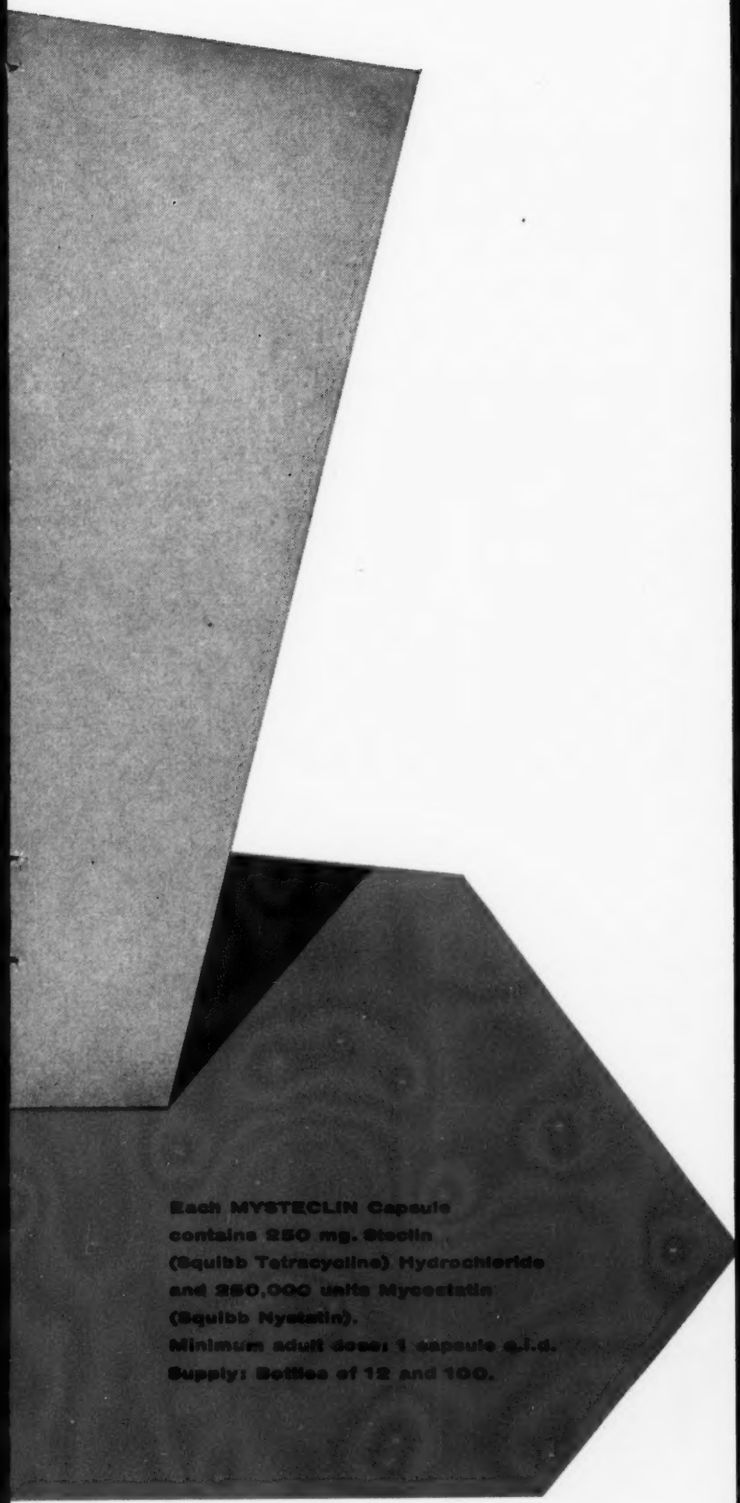
Because it contains Mycostatin (Squibb Nystatin), the first safe antifungal antibiotic, MYSTECLIN acts to prevent monilial overgrowth frequently observed during broad spectrum antibiotic therapy. Manifestations of this overgrowth may include some of the diarrhea and anal pruritus associated with antibiotic therapy, as well as vaginal moniliasis and thrush. On occasion, serious and even fatal infections caused by monilia may occur.

Mysteclin

STECLIN-MYCOSTATIN

(SQUIBB TETRACYCLINE-NYSTATIN)

"MYSTECLIN", "STECLIN" AND "MYCOSTATIN" ARE SQUIBB TRADEMARKS



Each MYSTECLIN Capsule contains 250 mg. Steclin (Squibb Tetracycline) Hydrochloride and 250,000 units Mycostatin (Squibb Nystatin).
Minimum adult dose: 1 capsule q.i.d.
Supply: Bottles of 12 and 100.

SQUIBB

A PARTIAL LIST OF INDICATIONS FOR MYSTECLIN

When caused by tetracycline-susceptible organisms, the following conditions are among those which may be expected to respond to Mysteclin:

Abscess
Bronchiectasis
Bronchitis
Bronchopneumonia
Burns, Infected
Cellulitis
Cervicitis
Chancroid
Colitis
Cystitis
Diarrheas, Infectious
Diphtheria
Dysentery, Amebic
Dysentery, Bacillary
Empyema
Endocarditis, Bacterial
Epididymitis
Erysipelas
Furunculosis
Gangrene
Gastroenteritis
Gonorrhea
Granuloma Inguinale
Klebsiella Pneumonia
Laryngitis
Lymphadenitis
Lymphangitis
Lymyphogranuloma Venereum
Mastoiditis
Meningitis
Metritis
Osteomyelitis
Otitis Media
Peritonitis
Pertussis
Pharyngitis
Pinworm Infestation
Pneumonia
Psittacosis
Pyelonephritis
Q Fever
Rocky Mountain Spotted Fever
Salpingitis
Scarlet Fever
Scrub Typhus
Sepsis, Puerperal
Septic Sore Throat
Septicemia
Sinusitis
Skin Graft Infections
Surgical Prophylaxis
Tonsillitis
Tracheobronchitis
Tularemia
Typhoid Fever
Typhus
Urethritis
Vesiculitis
Vincent's Infection
Wounds, Infected
Yaws

It is impossible to predict with certainty in which patients clinical moniliasis may develop as a result of broad spectrum antibiotic therapy. However, the added protection afforded by Mysteclin against monilial superinfection is especially important in patients who are debilitated, elderly, or diabetic, or when antibiotic therapy must be prescribed in high dosage or for prolonged periods. It is also important in infants (particularly prematures), as well as in patients for whom concomitant cortisone or related steroid therapy is prescribed, or in subjects who have developed a monilial complication on previous broad spectrum therapy.

Mysteclin is particularly useful in women, inasmuch as they not infrequently develop vulvovaginal moniliasis after treatment with ordinary broad spectrum antibiotics; this is especially common in women who are pregnant or diabetic.

for the pain and disability of **HERPES ZOSTER**

PROTAMIDE®

(SHERMAN)

published studies show:*

Improvement is "almost immediate," with "good to excellent results" in four out of five patients, and no postherpetic neuralgia in any patient who responded favorably.

Protamide is a sterile colloidal solution prepared from animal gastric mucosa . . . denatured to eliminate protein reaction . . . completely safe and virtually painless by intramuscular injection.

Clinical data on request.

use **PROTAMIDE®** *first*

in herpes zoster and post-infection neuritis

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS

*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

In 30 minutes–
antibacterial
action begins

In 24 hours–
turbid urine
usually clear

*"...it appears that Furadantin is one of the most effective single agents available at this time."**

Furadantin®

BRAND OF NITROFURANTOIN

IN
URINARY
TRACT
INFECTIONS

- specific affinity for the urinary tract produces high antibacterial concentrations in urine in minutes—continuing for hours
- hundreds of thousands of patients treated safely and effectively
- rapidly effective against a wide range of gram-positive and gram-negative bacteria, including many strains of Proteus and Pseudomonas species and organisms resistant to other agents
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- no cases of monilial superinfection ever reported

SUPPLIED: Tablets, 50 and 100 mg. in bottles of 25 and 100.
Oral Suspension, 5 mg. per cc. bottle of 118 cc.

*Breakey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. *54*: 805, 1955.

EATON LABORATORIES, Norwich, N.Y. **NITROFURANS** a new class of antimicrobials neither antibiotics nor sulfas

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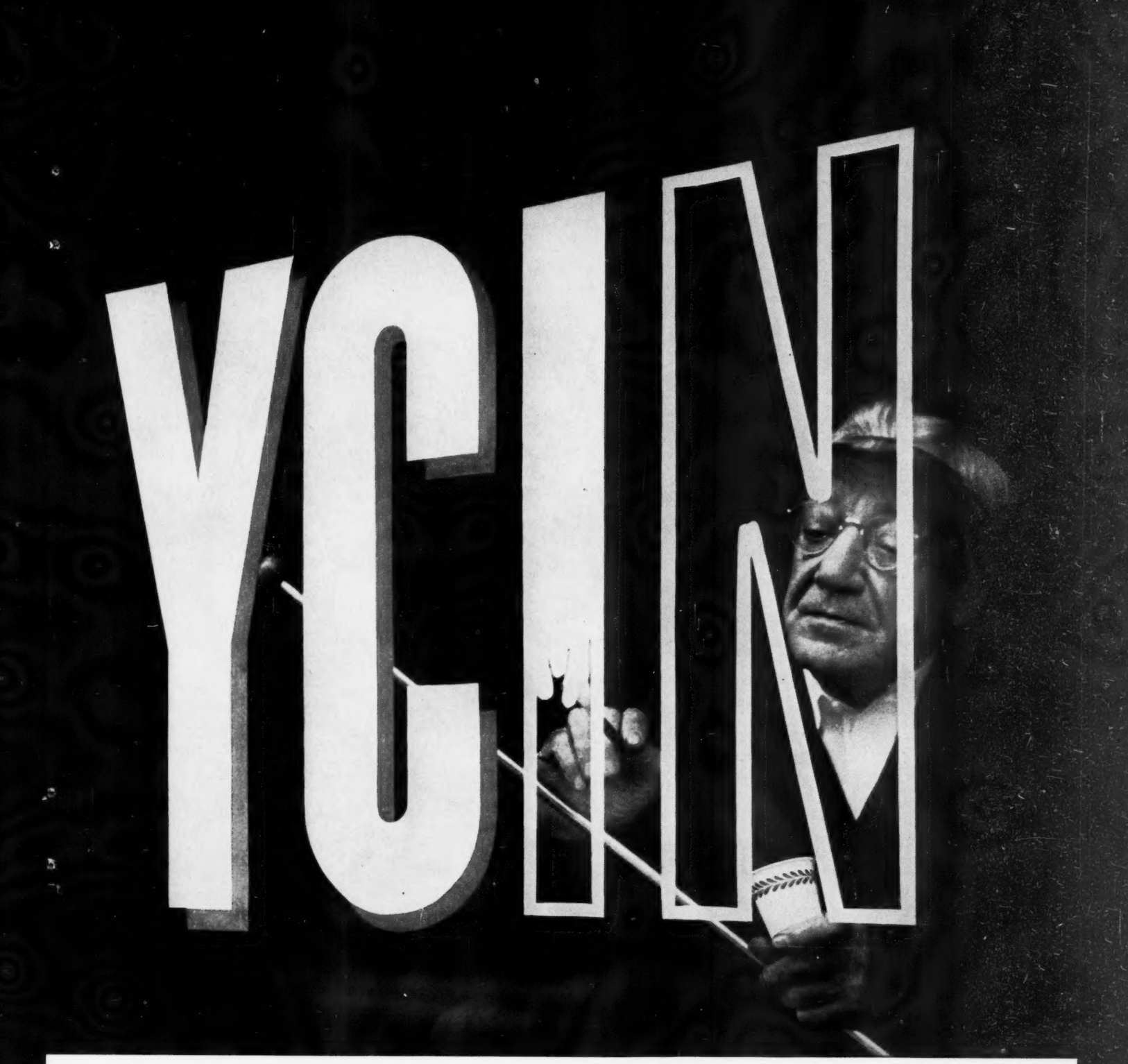
ACHROMYCIN*

Tetracycline *Lederle*

widely prescribed because of these important advantages:

1) rapid diffusion and penetration
2) prompt control of infection
3) true broad-spectrum activity (proved effective against a wide variety of infections caused by Gram-positive and Gram-negative bacteria, rickettsiae, and certain viruses and protozoa)
4) negligible side effects
5) every gram produced in Lederle's *own* laboratories under rigid quality control, and offered *only* under the Lederle label
6) a *complete* line of dosage forms



in prolonged illness, prescribe

ACHROMYCIN SF

TETRACYCLINE with STRESS FORMULA VITAMINS

Attacks the infection, bolsters the body's natural defense. Stress vitamin formula suggested by the National Research Council in *dry-filled, sealed* capsules with ACHROMYCIN, 250 mg. Also available: ACHROMYCIN SF ORAL SUSPENSION (Cherry Flavor), 125 mg. per 5 cc. plus vitamins.

filled sealed capsules

(a Lederle exclusive!) for more rapid and complete absorption. No oils, no paste, tamperproof!

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filmtab

Nembu-Serpïn

TRADEMARK

round-the-clock sedation plus tranquilization

The combination of 30 mg. (½ gr.) Nembutal Calcium (Pentobarbital Calcium) and 0.25 mg. reserpine in each tiny Nembu-Serpin Filmtab provides longer-lasting sedation—without drowsiness— than Nembutal alone, plus a more rapid onset of tranquilizing effect than reserpine alone.

- short-acting Nembutal quickly induces drowsiness at bedtime, followed by refreshing sleep.
- longer-acting reserpine calms patients through the following days, yet they keep their drive and energy.

Faster-acting—no waiting for cumulative response. Anxiety and hypertension patients experience almost immediate relief as Nembu-Serpin's sedative-tranquilizing action rapidly takes effect.

Smaller dosages—fewer side effects. Small dosages make side effects rare, medication economical, dosage schedules simple. Just one Nembu-Serpin Filmtab at bedtime will calm the worries of most anxiety patients. In bottles of 100 and 500 Filmtabs.

Abbott

*Film-sealed tablets.

Full Diuretic Control with Fewer Injections

The THIOMERIN program combines parenteral and suppository therapy to solve a major diuretic problem—drastic diuresis, patient alternately dry and waterlogged.

Parenteral THIOMERIN initiates diuresis . . . supplemented by THIOMERIN Suppositories to permit maximal spread between injections, to prevent fluid accumulation, and to maintain dry weight. Together, they offer a well-tolerated and convenient regimen for smooth edema control.[1]

Supplied: THIOMERIN Suppositories, boxes of 12. Injection THIOMERIN Solution, vials of 2 cc., boxes of 12; vials of 10 cc. Injection THIOMERIN (lyophilized), vials of 1.4 Gm. (10 cc. upon reconstitution) and 4.2 Gm. (30 cc. upon reconstitution).

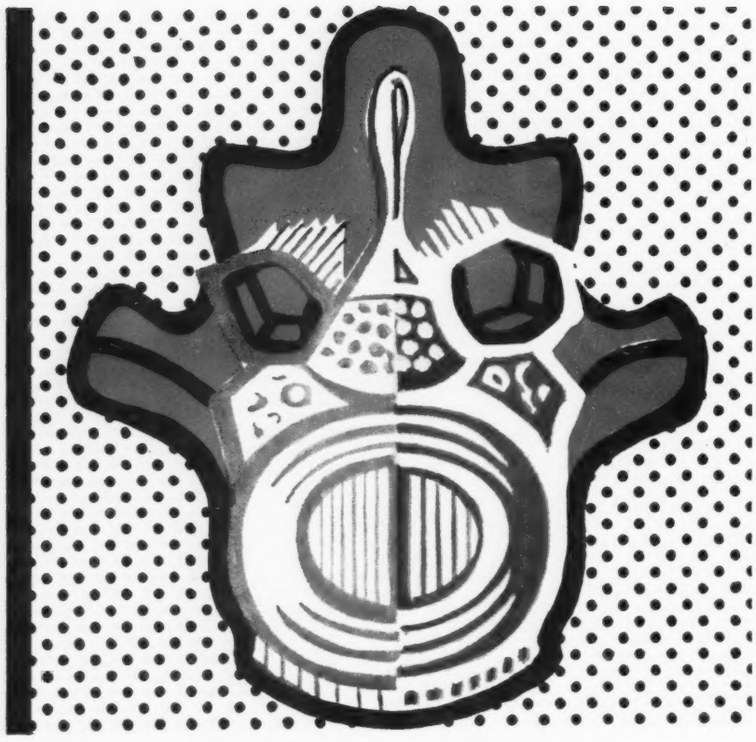
1. Daly, J.W.: Am. J. M. Sc. *228*:440 (Oct.) 1954.

INJECTION RECTAL SUPPOSITORIES

THIOMERIN® Sodium

MERCAPTOMERIN SODIUM

in arthritis
and
allied disorders...



nonhormonal anti-arthritic

BUTAZOLIDIN®

(brand of phenylbutazone)

relieves pain • improves function • resolves inflammation

Employing the serum protein-polysaccharide ratio (PR) as an objective criterion of rheumatoid activity, it has again been shown that BUTAZOLIDIN "...produces more than a simple analgesic effect in rheumatoid arthritis."[1]

Clinically, the potency of BUTAZOLIDIN is reflected in the finding that 57.6 per cent of patients with rheumatoid arthritis respond to the extent of "remission" or "major improvement."[2]

Long-term study has now shown that the failure rate with BUTAZOLIDIN in rheumatoid arthritis, and particularly in rheumatoid spondylitis, is significantly lower than with hormonal therapy.[3]

(1) Payne, R. W.; Shetlar, M. R.; Farr, C. H.; Hellbaum, A. A., and Ishmael, W. K.: J. Lab. & Clin. Med. *45*:331, 1955. (2) Bunim, J. J.; Williams, R. R., and Black, R. L.: J. Chron. Dis. *1*:168, 1955. (3) Holbrook, W. P.: M. Clin. North America *39*:405, 1955.

BUTAZOLIDIN® (brand of phenylbutazone). Red coated tablets of 100 mg.

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with its use are urged to send for literature before instituting therapy.

GEIGY PHARMACEUTICALS Division of Geigy Chemical Corporation
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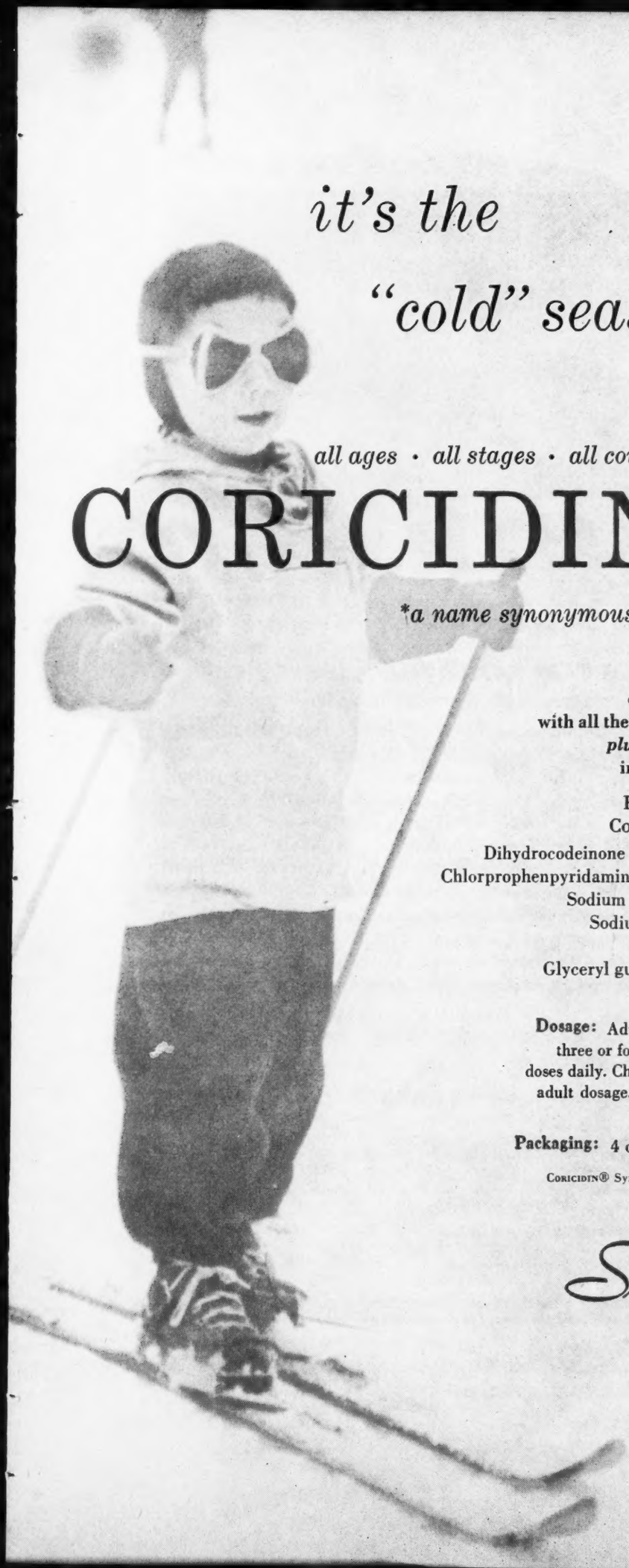


it's the

"cold" season...

all ages · all stages · all coughs · respond to

CORICIDIN* *Syrup*

**a name synonymous with cold control*

one versatile preparation
with all the advantages of CORICIDIN
***plus* superior cough control**
in a pleasant-tasting syrup

Each teaspoonful (5 cc.) of
CORICIDIN Syrup* contains:

Dihydrocodeinone bitartrate	1.67 mg.
Chlorprophenpyridamine maleate	2 mg.
Sodium salicylate	225 mg.
Sodium citrate	120 mg.
Caffeine	30 mg.
Glyceryl guaiacolate	30 mg.

*Exempt narcotic.

Dosage: Adults—One teaspoonful every three or four hours not exceeding four doses daily. Children 6-12 years—One-half adult dosage. Younger children—Adjust dosage according to age.

Packaging: 4 oz., pint, and gallon bottles.

CORICIDIN® Syrup, brand of antitussive-analgesic.

Schering

CN-J-54

new...paired piperidol action
for functional gastrointestinal complaints

rapid
visceral eutonic, Dactil®

prolonged
cholinolytic, Piptal®

relief throughout the G. I. tract

Tridal

TRIDAL permits more comprehensive control of gastrointestinal complaints by providing the combined benefits of two piperidols. The local action of Dactil* works immediately to give **rapid** relief of gastrointestinal pain and spasm; the potent cholinolytic Piptal† reinforces relief and provides **prolonged** normalization of secretion and motility.

TRIDAL is singularly free from urinary retention, constipation, dry mouth, blurred vision.

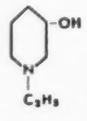
dosage: One TRIDAL Tablet two or three times a day and at bedtime. Unless rapidly swallowed with water, TRIDAL will produce some lingual anesthesia.

Each TRIDAL Tablet contains 50 mg. of Dactil and 5 mg. of Piptal. Bottles of 50 compressed, uncoated tablets.

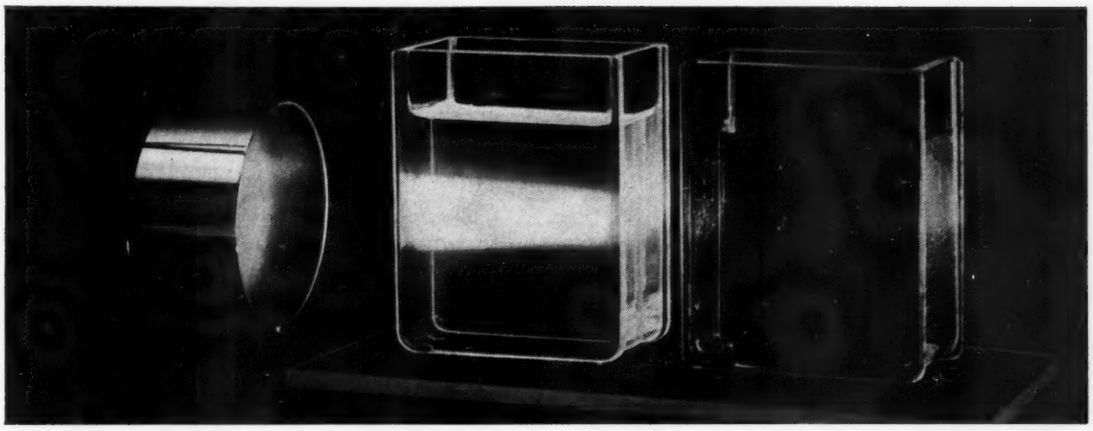
*Dactil (the *only* brand of N-ethyl-3-piperidyl diphenylacetate hydrochloride): the piperidol to prescribe alone when no interference with digestive secretion is desired.

†Piptal (the *only* brand of N-ethyl-3-piperidyl-benzilate methobromide): the piperidol to prescribe alone when peptic ulcer is known to be present and normalization of secretion as well as motility is desired.

Lakeside Laboratories, Inc. PIONEERS IN PIPERIDOLS MILWAUKEE 1, WISCONSIN



THIRD REPORT



ANOTHER HIGHLIGHT ON LECITHIN – A NATURAL PHOSPHATIDE

Phosphatides – Clearing Agents of Blood Plasma

Phosphatides have been found in all vegetable and animal cells. There seems little doubt that they are part of the basic structure of protoplasm and also enter into cell metabolism. The most abundantly found phosphatides are the lecithins, whose surface active properties, when combined with proteins and carbohydrates, play an important role as physiologic emulsifiers of fats and oils.[1]

The following considerations highlight the importance of *adequate lecithin plasma concentrations.*

Phosphatides together with cholesterol are found in plasma in combination with proteins and circulate as lipoproteins.[2] The phosphatides in plasma protein are believed to be highly essential for the stability of the complex colloidal system represented by blood plasma.[3] A phosphatide content of 30% or more seems necessary to keep the plasma clear and non-lipemic;[2] lower concentrations will cause the plasma to remain cloudy. (In human plasma lecithin makes up about 80% of the phosphatides present; others are sphingomyelin and cephalin.[2]) A constantly cloudy, lipemic serum can be considered a sign of disturbed fat metabolism, which has been incriminated in the pathogenesis of many serious disturbances. Research on lecithin's potentially useful role in the management of the more complicated forms of deranged lipid and cholesterol metabolism – as in essential hyperlipemia, idiopathic familial hypercholesteremia, xanthomatosis and diabetes – is now being actively conducted. If you are interested in the progress of this research or if you desire to have clinical trial supplies, won't you write to us?

An excellent source of lecithin is Glidden's "RG" Oil-free Soya Lecithin, a highly purified extract containing a minimum of 95% phospholipids. It is packed in a specially designed 8 oz. container to maintain its purity and freshness and is available at your drugstore.

Investigators of lecithin have used quantities from 7.5 to 30 grams daily in divided doses (3 teaspoonfuls equal 7.5 grams).

Administration: "RG" Lecithin is presented in palatable granules which may be taken plain, in milk, in orange juice or other citrus juice, or sprinkled on cereal.

Literature available on request.

Bibliography: 1. West, E. S., and Todd, W. R.: Textbook of Biochemistry, New York, The Macmillan Company, 1952, p. 184. • 2. Drill, V. A.: Pharmacology in Medicine, New York, McGraw-Hill Book Company, Inc., 1954, p. 64/6. • 3. Ahrens, E. H., Jr., and Kunkel, H. G.: J. Exper. Med. *90*:409 (Nov. 1) 1949.

GLIDDEN RG® LECITHIN

THE GLIDDEN COMPANY • CHEMURGY DIVISION
1825 North Laramie Avenue, Chicago 39, Illinois

QUALITY Glidden PRODUCTS

H+ OH−

Superior antacid action and...

"For palatability, many patients prefer Maalox"[1]

MAALOX®, an efficient antacid suspension of magnesium-aluminum hydroxide gel, is smooth-textured, and always pleasant to take. MAALOX was tested by thousands of hospital outpatients, who preferred it to other antacids. Indeed, *high patient acceptability* (without danger of constipation) is one of the outstanding advantages of MAALOX therapy.[2]

As to chemistry: MAALOX has more acid-binding capacity than aluminum hydroxide gel, and maintains its antacid effect twice as long.[3]

Supplied: *Suspension*, bottles of 12 fluidounces. *Tablets*, bottles of 100. Samples sent promptly on request.

1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

For Pain
try Ascriptin Tablets
(Aspirin buffered with Maalox)
- Doubles blood salicylate level
- Action more prolonged
- High gastric tolerance level
- Clinically proved.

Samples on request.

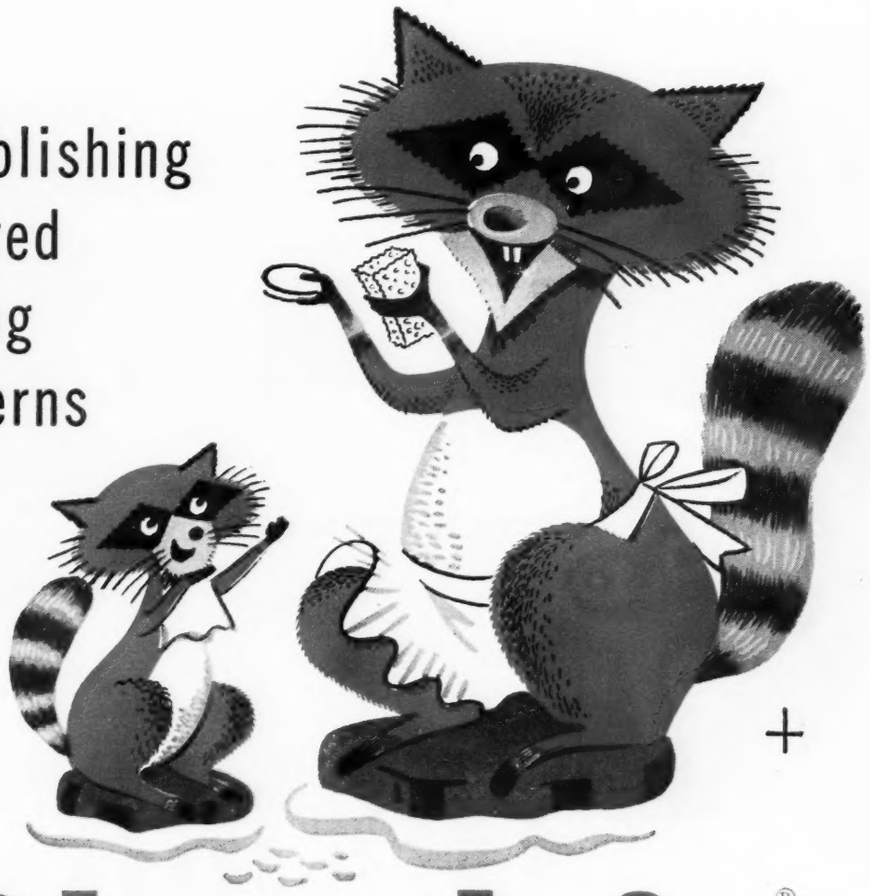
Ascriptin

Maalox®

"... better suited for antacid therapy"[2]

WILLIAM H. RORER, Inc. PHILADELPHIA, PA.

establishing
desired
eating
patterns



Obedrin®

and the 60-10-70 Basic Plan

In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct., 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE

When you want to control edema think first of

Diamox*

Acetazolamide Lederle

A nonmercurial oral diuretic. Acts by inhibiting the enzyme carbonic anhydrase. Produces prompt, ample diuresis lasting from six to twelve hours. Morning dosage allows an uninterrupted night's sleep. Well-suited to long-term use. Nontoxic. The most widely prescribed drug of its kind!

Indicated in cardiac edema, epilepsy, acute glaucoma, premenstrual tension, edema associated with toxemia of pregnancy and edema caused by certain types of electrolytic imbalance. Offered in scored tablets of 250 mg. for oral use, and in ampuls of 500 mg. for parenteral use in critical cases.

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Ferrous Iron with Vitamin C

for *simple*
specific
rapid
economical

correction of iron deficiency anemias

"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid . . ."*

"CYTOFERIN"—*the logical combination for iron therapy.*

- Iron in the readily absorbed ferrous form.
- Vitamin C to maintain acidity in the upper intestinal tract for greater iron absorption.
- Vitamin C as a reducing agent for the ferric iron obtained from food.
- Vitamin C for hypochromic microcytic anemias, which will not respond to oral iron therapy alone.

"CYTOFERIN"—*the direct approach to greater iron absorption.*

Each tablet contains:
Ferrous sulfate exsic. (3 gr.).....200 mg.
Vitamin C (ascorbic acid).....150 mg.

Dosage: 1 tablet two or three times daily, taken preferably with meals.

Supplied: No. 705, bottles of 100 and 1,000.

NEW PRODUCT

*Sacks, M. S.: Ann. Int. Med. *42*:458 (Feb.) 1955.

Ayerst

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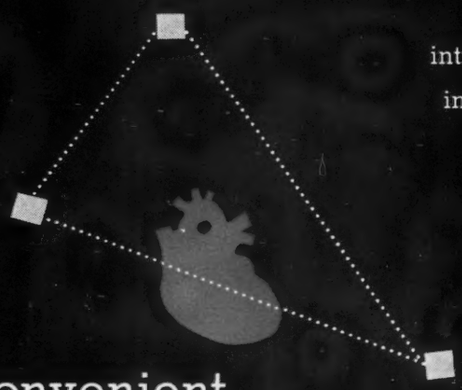

most convenient digitalis preparation . . . change route any time without changing dose or interval

DIGITALINE NATIVELLE®

Now with Digitaline Nativelle Intramuscular, a complete range of routes of administration is available. This preparation—specifically designed for I.M. use—avoids irritation often encountered when I.V. forms are administered intramuscularly. The dosage schedule with DIGITALINE NATIVELLE need never be changed because of change in the route of administration. The same advantages are provided by all forms, enabling the physician to cope with any change in the patient's status. Prescribe DIGITALINE NATIVELLE—the original pure crystalline digitoxin • pure active principle • complete absorption • rapid onset of action • smooth, even maintenance • frequent dosage readjustment unnecessary • virtual freedom from gastric upset

Consult your Physicians' Desk Reference for dosage information.

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a rational, conservative way
to help check

internal bleeding

associated with abnormal capillary permeability and fragility in

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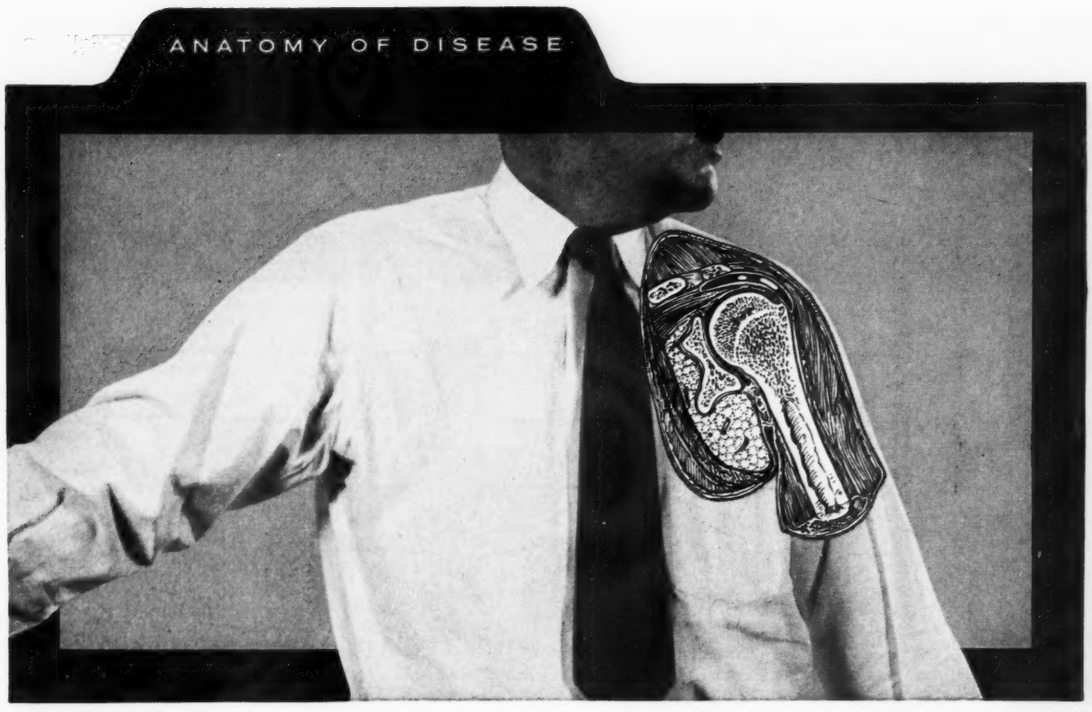

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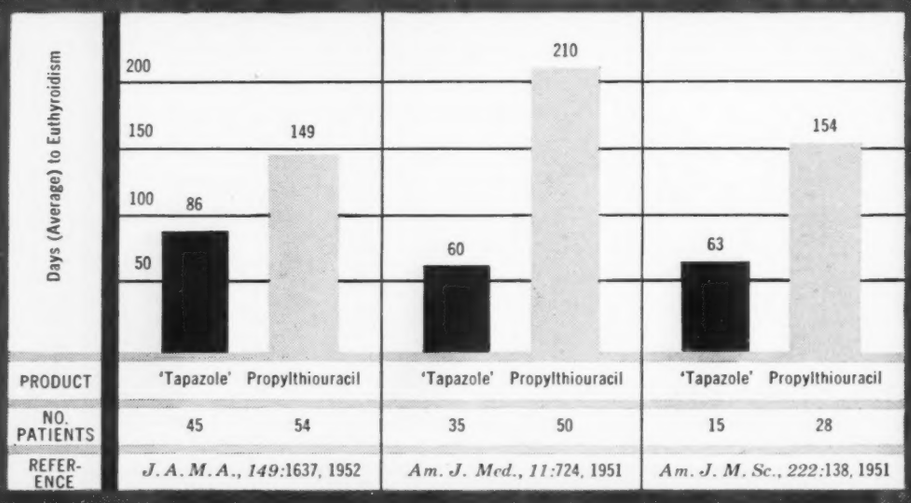

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*J. Clin. Endocrinol., 14:948, 1954.

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Editorial

On the "Turnover" of Plasma Proteins

THE purpose of this article is to discuss several problems incident to determination of the "turnover rate" of plasma proteins. The difficulties may be illustrated by reference first to serum albumin.

By "turnover rate," as applied to any substance of biologic interest, is meant the amount of that substance which is utilized and replaced by the organism in unit time. Turnover rates are determined through the use of isotopically labelled compounds N^{15}, C^{14}, S^{35} and I^{131} being commonly employed for studies in protein metabolism.* Substantially the same information is conveyed by the biologic half-life of the labelled compound, the calculation of this being based upon an extrapolation to zero time of the terminal "linear" portion of a curve in which the logarithm of the specific activity (or counts per minute per unit volume of blood) is plotted against time after administration of the isotope. In the case of serum albumin use is commonly made of a preparation that has been biologically labelled with I^{131} or S^{35}.

Serum Albumin. To start with I propose to concentrate on serum albumin and to indicate how the studies might be conducted if one were free to do so without compromise. Later, I shall discuss some of the shortcuts, assumptions and compromises that are commonly made in such investigations. First, as the experiment is begun; the serum albumin pool must be measured. This may be done, in principle, by the intravenous injection of a known amount of pure labelled serum albumin of known specific activity, withdrawal shortly thereafter of a sample of blood, preparation therefrom of a specimen of pure serum albumin, determination anew of the specific activity and, from the dilution in activity that has resulted, proceeding by simple arithmetic to a calculation of the size of the serum albumin pool. If, in the hours or days that follow, we have reason to believe that the pool size may have changed, a terminal determination of the serum albumin pool will be made. Probably, albumin-I^{131} may not be used for this second determination, because of the albumin-I^{131} already in the circulation, but albumin-S^{35} may be employed: differential determination of S^{35} and I^{131} presents no serious problems. If the pool has altered in size, an appropriate correction will be attempted. Meanwhile, albumin-I^{131} will be undergoing metabolism, and replacement by ordinary unlabelled albumin will be taking place. Exchange will be proceeding between the proteins of the intravascular and extravascular pools. If and when an equilibrium is established, an excess of albumin in one pool or the other will result in a movement of albumin into the pool which is temporarily deficient therein.[1] Samples of blood will be drawn from time to time, perhaps daily, and after isolation of "pure" albumin the specific activity will in each instance be determined. The logarithm of the specific activities will next be plotted against time after a correction has been made for such shrinkage or expansion in pool size as may have ensued. Extrapolation of the terminal linear portion of the curve to zero time will now permit the usual calculation of the turnover rate or biologic half-life.

* In most of the discussion that follows, reference is made only to radioactive isotopes; the same considerations apply, however, to stable isotopes.

[1] GITLIN, D. and JANEWAY, C. A. *Science*, 118: 301–302, 1953.

Other Plasma Proteins. If the turnover rates of other plasma proteins are to be determined, similar procedures would be followed. The use of "pure" individual globulins (and other proteins), suitably labelled, is essential. The isolation of individual "pure" specimens of the desired proteins and determination of their specific activities would follow. Again the necessary precautions would be taken to assure that a steady state is maintained (replacement equals utilization), i.e., that the pool sizes remain unchanged. Should these change in the course of the experiment, the necessary corrections would be attempted.

Assumptions, Compromises, Short Cuts. This is where the troubles begin.

1. Were an albumin to be ideally labelled for a turnover experiment the metabolic fate of the preparation, at least its rate of utilization, would be identical with that of native serum albumin. At the same time, ideally, the metabolic products would not enter the amino acid pool or any other pools that may participate in protein synthesis. Re-utilization of the isotope (recycling) should be insignificant.

When albumin-C^{14}, N^{15} or S^{35} is used there is, one may safely presume, little doubt but that the labelled preparation will suffer the same metabolic fate, at the same rate, as unlabelled albumin. One measures, of course, the rate of disappearance of the "label" from the "albumin pool" and there can be no guarantee that the metabolic products which will contain the S^{35}, C^{14} or N^{15} will disappear from the albumin pool at the same rate. This means that turnover rates may be very dependent upon the label used.

2. One can be reasonably sure that recycling will constitute a serious problem in experiments in which albumin-S^{35}, C^{14} or N^{15} is employed. It is common practice to minimize this source of error by the administration of relatively large quantities of unlabelled cystine, methionine or such other amino acids which, by entry into the amino acid pool, will dilute out the labelled amino acid released from the protein during metabolism. How effective this device is cannot be determined. Is it not probable that the relatively long "life" reported for albumin-S^{35} (as compared with albumin-I^{131}) is due to recycling of the S^{35} amino acids?

3. As for albumin-I^{131} a rather involved situation exists. The iodinated albumin which is reported upon in some papers contains only 1 to 2 atoms of iodine per mole of albumin. If the protein were fully iodinated and if the iodine entered the tyrosine residues, as is commonly conceded, to give residues of 3,5-diiodotyrosine, 34 atoms of iodine would be taken up per mole of albumin. Berson used a product with an iodine content of 1.6 atoms per mole and, in one experiment, a "heavily iodinated" product which contained 11.1 atoms per mole.[2] While the latter gave some evidence of heterogeneity on electrophoresis, the former gave but a single symmetrical peak on ultracentrifugal and electrophoretic analysis. This does not necessarily mean that lightly iodinated albumin (which is commonly used) has the same physiochemical properties as unlabelled albumin; actually it would be quite easy for a 5 per cent admixture of fully iodinated albumin in native serum albumin to escape detection by such methods.

This in turn raises the question whether such an iodoalbumin is a fairly uniform product, consisting only of molecules which are identically labelled at the level of 1 or 2 atoms of iodine per molecule; or is it a mixture of 95 per cent native albumin and 5 per cent fully iodinated albumin; or, between these two extremes, does it consist of a wide spectrum of iodoalbumins which contain anywhere from zero to 34 atoms of iodine per molecule? The answer to this, although difficult to ascertain, is of some consequence for it is possible that very heavily iodinated molecules would not be received by the enzyme systems involved in protein catabolism with the same abandon as very lightly iodinated molecules. This would have some effect on turnover rates. Indeed Berson et al. noted that a heavily iodinated product (11.1 atoms of iodine per molecule) had a half-life of eleven days whereas the lightly iodinated material (1.6 atoms of iodine per molecule) gave a half-life of sixteen days.[2]

4. Involved also is the fate of the iodine. Is the iodoalbumin deiodinated prior to hydrolysis and metabolic use or is it first split into constituent amino acids (plus diiodotyrosine) or larger fragments prior to release of the iodine? While there is good reason for believing that the I^{131} that disappears from the blood may be satisfactorily accounted for in the urine,[2] there are reasonable grounds for concern when the course of metabolism of the iodoalbumin is so obscure.

5. Fortunately with iodoalbumin there need be no worry about recycling: (a) as fast as the

[2] Berson, S. A., Yalow, R. A., Schreiber, S. S. and Post, J. *J. Clin. Investigation*, 32: 746–768, 1953.

I^{131} is lost from the blood it appears in the urine and is unavailable for reutilization; (b) even if iodotyrosine did remain in the blood for some time it seems improbable that it would be utilized in protein synthesis because of the presumed high specificity of the enzymes concerned. Lugol's solution is commonly administered, though with questionable value, to minimize the relatively small amount of recycling that might go on in the thyroid.

6. It is seldom indeed that "pure" iodoalbumin of a stated specific activity is injected. Sometimes whole labelled plasma from a donor dog is administered. Sometimes, at least with S^{35}, C^{14} or N^{15}, labelled yeast or a labelled amino acid is given orally. In these latter cases the situation can be a bit complicated: for example, the administered material must be so converted metabolically that the isotope is transferred to serum albumin in the recipient. This may be a prolonged process which would involve digestion, absorption and biosynthesis, all of which unfortunately becomes hopelessly entangled in time with the mixing phase.

7. This defeats any serious attempt to determine the size of the albumin pool which is in itself no simple matter as we shall presently see. We are now driven to the collection of blood samples at suitable time intervals during the experiment, fractionation therefrom of serum albumin (and possibly other proteins as well) and determination of their specific activities. By zone electrophoresis, if all goes well, a fairly clean resolution of serum albumin and of some of the other proteins or classes of proteins may be achieved. The use of central portions of the bands for analysis (protein and isotope concentrations) is indicated.* Even so, at least after intravenous iodoalbumin labelled *in vitro*, up to 20 per cent of the I^{131} may be found in the other protein bands.[3]

Under the best of conditions we shall thus end the experiment with a series of values for specific activities of the albumin (and possibly other proteins) or we may have a series of values for isotope concentrations expressed as counts per minute per unit weight of fraction. The logarithms of these values may now be plotted against elapsed time since initiation of the sampling. If a steady state is maintained (utilization equals replacement), with neither expansion nor contraction in pool size, such a plot should show a fairly rapid decrease at the beginning (the mixing phase) and an approach to rectalinearity thereafter (metabolic decay phase). By extrapolation of this linear portion to zero time and by the simple process of noting the time that corresponds with one-half of the zero-time specific activity (or equivalent thereof) a value may be derived which is said to be the biologic half-life. The real question is, does such a value have any significance especially in the absence of any proof that a steady state is maintained and in the absence of any meaningful information as to pool size? In the normal organism it may well be contended that our concepts of physiologic integrity necessarily presuppose that homeostatic mechanisms of one kind and another will preserve, for reasonable periods of time, both pool size and a steady state. But may such assumptions be defended in a serum albumin experiment that calls for massive hemorrhage, the injection of large quantities of plasma protein or of a protein hydrolysate, deliberate capillary damage, or a calculated insult to the kidney? Likewise are they tenable in clinical investigations in which we may have hypertension and edema, liver cirrhosis and large volumes of ascitic fluid, nephrosis and much loss of protein through the kidney, or in certain kinds of severe nutritional disease?

8. Now we come to the crucial problem of pool size. Ideally the serum albumin pool would be determined by the dilution technic after intravascular administration of labelled serum albumin. With iodoalbumin or T-1824 (which has a high specific affinity for albumin) Freinkel et al.[4] were able to establish that mixing in the central circulation (plasma flow rate of 3,750 ml./min.) is complete in thirteen to fifteen seconds. In the vessels of the lower extremities a mixing time of eighteen to twenty seconds was observed. However, the albumin pool is not restricted to the blood; other "compartments" exist which defy measurement either of number

* The requirements for purity of a protein are very exacting—so much so that they are seldom satisfied by any existing preparation. Recognition of the difficulties involved does not, however, appear to justify some of the grossly impure preparations that are commonly employed and assayed in research in this field. As a compromise it may be permissible to resort to zone electrophoresis for purification if all necessary precautions are taken. While possibly acceptable for albumin this procedure is still far from adequate for isolation of pure specimens of other plasma proteins.

[3] Armstrong, S. H., Jr., McLeod, K., Wolter, J. and Kukral, J. *J. Lab. & Clin. Med.*, 43: 918–937, 1954.

[4] Freinkel, M., Schreiner, S. E. and Athens, J. W. *J. Clin. Investigation*, 32: 138–148, 1953.

or of size. The data reported by Berson[2] permit, for mathematical analysis at least, the concept of one compartment with a mixing or equilibration phase wherein $T_{\frac{1}{2}}$ equalled two and a half hours and a second wherein $T_{\frac{1}{2}}$ equalled thirty-one hours. During the metabolic phase, the period of isotope disappearance, $T_{\frac{1}{2}}$ equalled eleven to twenty-five days (average of seventeen days for forty-six subjects). When active exchange takes place across the peritoneal membrane, as with ascites, equalization of specific activities on either side of the membrane may not be attained for ten days.[2] The times required for equilibration with albumin present in the liver, spleen and lymphoid tissue would probably defy determination.* Eisenmenger and Slater[5] report that the equilibration times for both albumin and γ-globulin are two and a half to six days except after intraperitoneal administration when equilibration required, in some cases, more than two weeks. Equilibration of labelled albumin, in the experiments reported by Armstrong et al.,[3] required one and a half to six days. The data of Freinkel et al.[4] are compatible with an equilibration time of three or four days. The equilibration time is, in part, determined by the species and, in part, by the nature of the substance administered.[6]

9. Possibly an approach to the problem of determining the albumin pool size may be made by using a labelled but metabolically inert product of about the same size and shape as serum albumin. Ideally, it would be amphoteric, and with a rather considerable number of positively and negatively charged groups (in almost equal number); it would, however, have a low dipole moment and would be capable of much hydration. In fact, ideally, it would differ from serum albumin only in its total resistance to proteolysis. Such a product would distribute itself between the various "compartments" but would not be metabolized: the equilibration phase would be completely isolated from any metabolic phase.

10. As for the turnover rate or the biologic half-life of albumin, the values reported in the literature cover a wide range, depending in part upon the isotope that has been used but also upon the duration of the experiment. In general, $T_{\frac{1}{2}}$ extends from nine or ten days to over 200 days, with many of the values clustered around twenty days for iodoalbumin and thirty-five days for albumin-S^{35}. If the experiment is of short duration (nine or ten days), serious errors may enter because of uncertainties in determining with sufficient precision the slope of the terminal rectalinear portion of the curve. Thus Freinkel et al. "break" the curvilinear part of a certain plot at the four-day value but subsequent points are such that one would be equally justified in "breaking" the curve at the three-day value. By so doing the straightline portion is steepened and the apparent half-life is reduced.

11. A brief comment about the sizes of the "compartments" is in order. In a specific case (cirrhosis with ascites) Berson and Yalow[7] calculated that at the beginning of the study (twenty-two days' duration) 137 gm. of albumin were in the plasma, 217 gm. in the ascitic fluid and 157 gm. in the extravascular space. It is fair to conclude that in a normal individual much of the exchangeable albumin is in extravascular compartments. Berson et al.[2] calculate the total distribution space for serum albumin to be about two and a half times the plasma volume. The authors[7] comment on the difficulties in analysis imposed in all such turnover studies by lack of a steady state and on the further errors that arise if the extravascular spaces are reduced to a single compartment, or if they be ignored, or if consideration is not given to changes in pool size.

12. The dubious status of turnover studies as they apply to various substances of biologic interest, including plasma proteins, has been well discussed by Fisher;[8] and Zilversmit et al.[9] have pointed out some of the very essential precautions that must be taken if value may be attached to the results that emerge from such

* Krieger, H. et al. (*Proc. Soc. Exper. Biol. & Med.*, 73: 124–126, 1950) report in dogs that while a negligible proportion of albumin-I^{131} passes into the thoracic duct lymph in ten minutes the activity of the chyle per milliliter attains 40 to 50 per cent of the corresponding value for plasma within two hours. Cope and Moore (cited by Krieger) found for lymph and plasma an equilibration time of six to seven hours following intravenous injection of radioactive protein.

[5] Eisenmenger, W. J. and Slater, R. J. *J. Clin. Investigation*, 32: 564, 1953.

[6] Markus, M. and Feigen, G. A. *Am. J. Physiol.*, 180: 115–117, 1955.

[7] Berson, S. A. and Yalow, R. A. *J. Clin. Investigation*, 33: 377–387, 1954.

[8] Fisher, R. B. Protein Metabolism. London, 1954. Methuen & Co.

[9] Zilversmit, D. B., Entemman, C., Fishler, M. C. and Chaikoff, I. L. *J. Gen. Physiol.*, 26: 333, 1943.

studies. A quotation from Armstrong et al.[10] focuses sharply upon some of the difficulties: " . . . as usually estimated from "die away" semilogarithmic isotopic plots, the apparent turnover time implies constant and equal rates of synthesis and degradation during the experimental period. An increase in synthesis without comparable simultaneous increase in degradation will lead to steepening of slope and consequently a temporary shortening of the "time" by reason of progressive dilution of the isotopically labelled protein. A temporary increase in degradation without corresponding increase in synthesis could be graphically indistinguishable in terms of isotopic data alone. Differentiation is possible only in terms of a change in the total amount of component under study which may or may not be affected by a change in its concentration in plasma."

CONCLUSIONS

1. Although the purpose of this discussion has been to point out the difficulties that beset those who are doing research in this field it is not my intent to belittle the importance of the problem. There are many conditions of great clinical interest in which the destruction, loss and replacement of the plasma proteins are of real moment: certain types of renal disease, heart disease, liver disease, hemorrhage and certain kinds of chronic malnutrition may be mentioned among the most conspicuous. Attempts are made to simulate some of these in experimental animals and in either case it is important to be able to determine the rate of physical loss and catabolic destruction of any of the plasma proteins that may be involved. By the same token the rate of regeneration of these proteins under stated conditions is equally imperative as a subject of study. Much more basic data need to be gathered, however, before some of these problems may be pursued with profit.

2. Many of the arguments presented apply to a diversity of studies in which the labelling is accomplished with isotopes, dyes, antigens or red cells. In some cases the reticuloendothelial system has such a high affinity for administered colloids that the latter appear to be irreversibly removed from the circulation. In such cases we have an extravascular sump, not a pool in equilibrium with other pools.

3. Studies on the turnover of the "total globulin fraction" appear to be quite meaningless, if only because of the diversity in structure and function of the constituent proteins. In fact, grave uncertainties attach to studies on individual globulins because of the almost insuperable difficulties of fractionation and purification.

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[10] ARMSTRONG, S. H., JR., KUKRAL, J., HERSHMAN, J., MCLEOD, K., WOLTER, J. and BRONSKY, D. *J. Lab. & Clin. Med.*, 45: 51–60, 1955.

Clinical Studies

Ebstein's Disease*

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EBSTEIN'S disease is a congenital cardiac anomaly in which the origin of the tricuspid valve is displaced downward into the right ventricle to divide it into two portions, a proximal portion forming part of the atrial cavity and a distal ventricular portion. Following Ebstein's[1] original description autopsy reports of other cases were recorded. In 1937 Yater and Shapiro[2] reviewed the literature and concluded that it would appear to be impossible to make the diagnosis during life. However, Engle et al.[3] in 1950 suggested, from a review of the clinical notes on three autopsy cases undiagnosed during life, that clinical diagnosis was possible and by 1954 Medd et al.[4] from a review of twenty-six cases of Ebstein's disease reported since 1948, were able to describe a clinical picture characteristic of this anomaly.

The purpose of this paper is to present four additional cases of Ebstein's disease recognised during life, in two of which the diagnosis was confirmed at autopsy, and to describe the characteristic clinical features of this anomaly.

CLINICAL FEATURES

Symptomatology. Cases I and III suffered from attacks of paroxysmal tachycardia for fourteen years and six months, respectively, before hospital admission. In both patients these attacks were accompanied with cyanosis and were usually terminated by vomiting. In Case I slurred speech and weakness of the right arm

TABLE I
CLINICAL FEATURES OF FOUR PATIENTS WITH EBSTEIN'S DISEASE

Case	Age and Sex	Systemic Blood Pressure in Arms (mm. Hg)	Central Cyanosis	Finger Clubbing	Dulness on Percussion to Right of Sternum	Auscultation of Second Sound in Pulmonary Area	Position of Apex Beat	Other Signs
I	51, F	130/100	During paroxysmal tachycardia	−	+	Quiet, single	6th left space anterior axillary line	−
II	15, M	145/100	Absent	−	+	Loud, split	5th left space mid-clavicular line	−
III	13, F	130/80	Absent	−	−	Single, quiet	6th left space mid-axillary line	Signs of constrictive pericarditis
IV	9, F	120/60	At rest	+	−	Loud, split	5th left space mid-clavicular line	Weak femoral pulse

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was also present during some of the attacks. All the patients were unduly breathless on exertion and in Cases I, II and III palpitation was also noted. Blueness of the lips was present from birth in Case IV. In Case I cyanosis was absent at rest but appeared during attacks of tachycardia.

TABLE II
ABNORMAL ELECTROCARDIOGRAPHIC FINDINGS IN FOUR PATIENTS WITH EBSTEIN'S DISEASE

Case	Paroxysmal Tachycardia	Ventricular Dominance	Axis	P-R Interval (sec.)	Peaked P Wave
I	+	Intermittent right bundle branch block	Horizontal	0.24	−
II	−	Intermittent right bundle branch block	Horizontal	0.16	+
III	+	Right	Vertical	0.20	+
IV	+ during cardiac catheterization	Left	Horizontal	0.14	+

Signs. In all cases there was a protodiastolic triple rhythm at the apex and a soft systolic murmur over the whole praecordium. This murmur was heard equally well in the mitral and pulmonary areas. In Case II there was marked splitting of the first heart sound in addition to the triple rhythm. No clinical evidence of pulmonary hypertension was noted in any of the patients in this series. Other clinical features are shown in Table I.

Electrocardiography. The abnormal electrocardiographic findings are shown in Figure 1 and Table II.

Radiology. The postero-anterior teleradiograms of the present group of patients are reproduced in Figure 2 and the abnormal radiologic findings are summarized in Table III.

Angiocardiography. This investigation was made in all four cases. Gross dilatation of the right atrium was apparent in every case and the contrast medium remained in the right side of the heart ten seconds after injection. (Fig. 3.) In Case IV a small right ventricle was outlined, while the pulmonary arteries were demonstrated only in Case III and were abnormally small. Early filling of the left atrium was seen in Case I.

Cardiac Catheterization. This investigation was carried out in Cases II, III, and IV and each time the catheter coiled up in a large right atrium. (Fig. 4.) In Cases III and IV this procedure produced runs of nodal tachycardia. Only in Case II was it possible to pass the catheter into the pulmonary artery. Other findings at cardiac catheterization are summarized in Table IV.

The haemoglobin levels and haematocrits of all four cases are shown in Table V.

AUTOPSY FINDINGS

CASE I. The heart weighed 500 gm. The medial and posterior leaflets of the tricuspid valve were displaced to an abnormal low position below the level of the annulus fibrosus and divided the right side of the heart into a small thick-walled myocardial chamber below and a huge thin-walled chamber above. The cavity of the small chamber below the tricuspid valve was smaller than the cavity of a normal right ventricle but its walls were hypertrophied. The thin-walled chamber consisted of the right atrium proper and a part of the right ventricle above the tricuspid valve

TABLE III
ABNORMAL RADIOLOGIC FINDINGS IN FOUR PATIENTS WITH EBSTEIN'S DISEASE

Case	Increase in Over-all Cardiac Size	Left Ventricular Enlargement	Prominent Right Border	Abnormal Pulsation of the Pulmonary Artery	Decreased Pulmonary Vascularity	Other Findings
I	Marked	..	+	−	+	Calcified tuberculous lesion at left apex
II	Moderate	+	+	−	+	−
III	Marked	..	+	−	+	Pericardial effusion
IV	Moderate	+	−	−	−	−

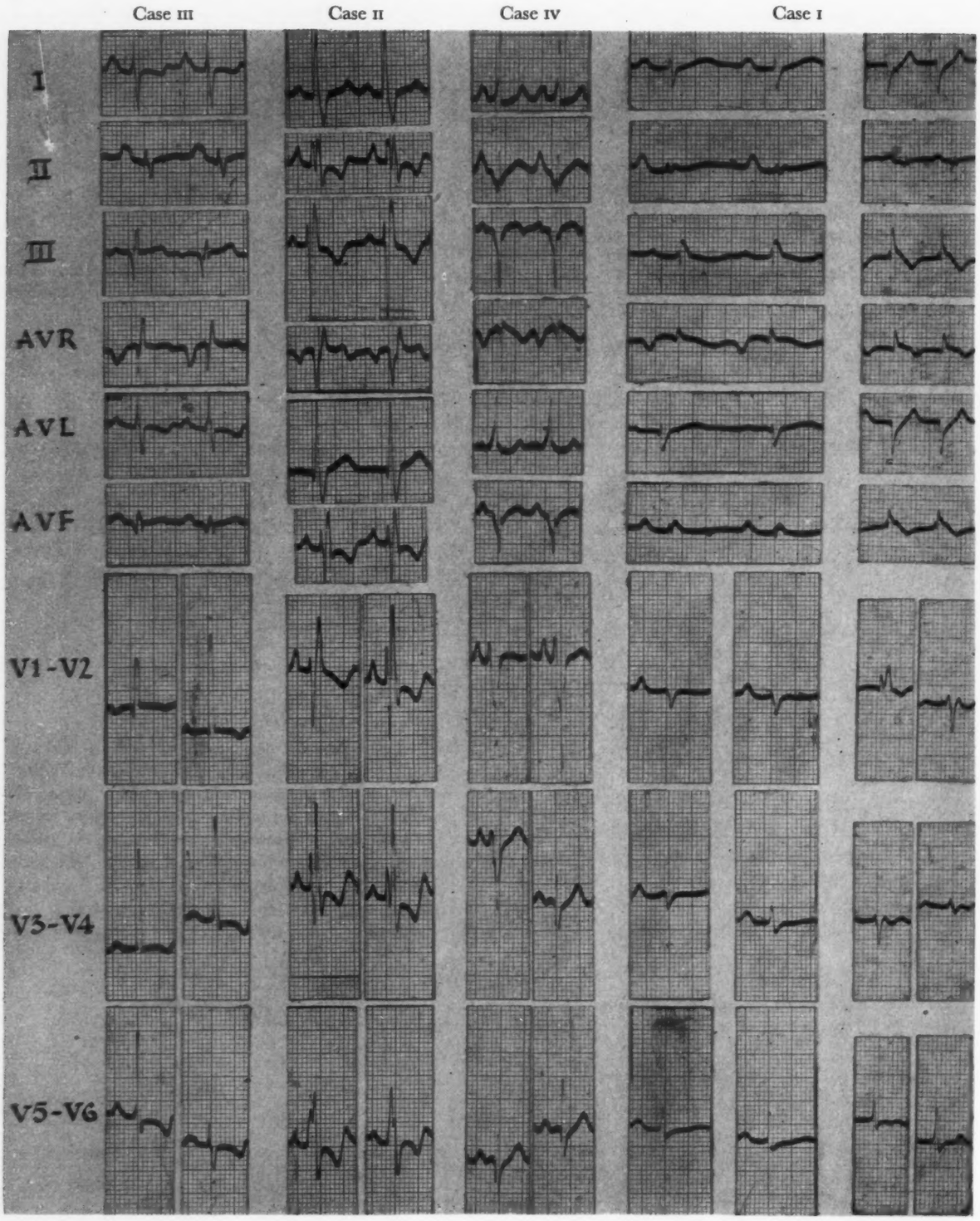


FIG. 1. Electrocardiograms of four cases in sinus rhythm and of Case I during an attack of paroxysmal tachycardia.

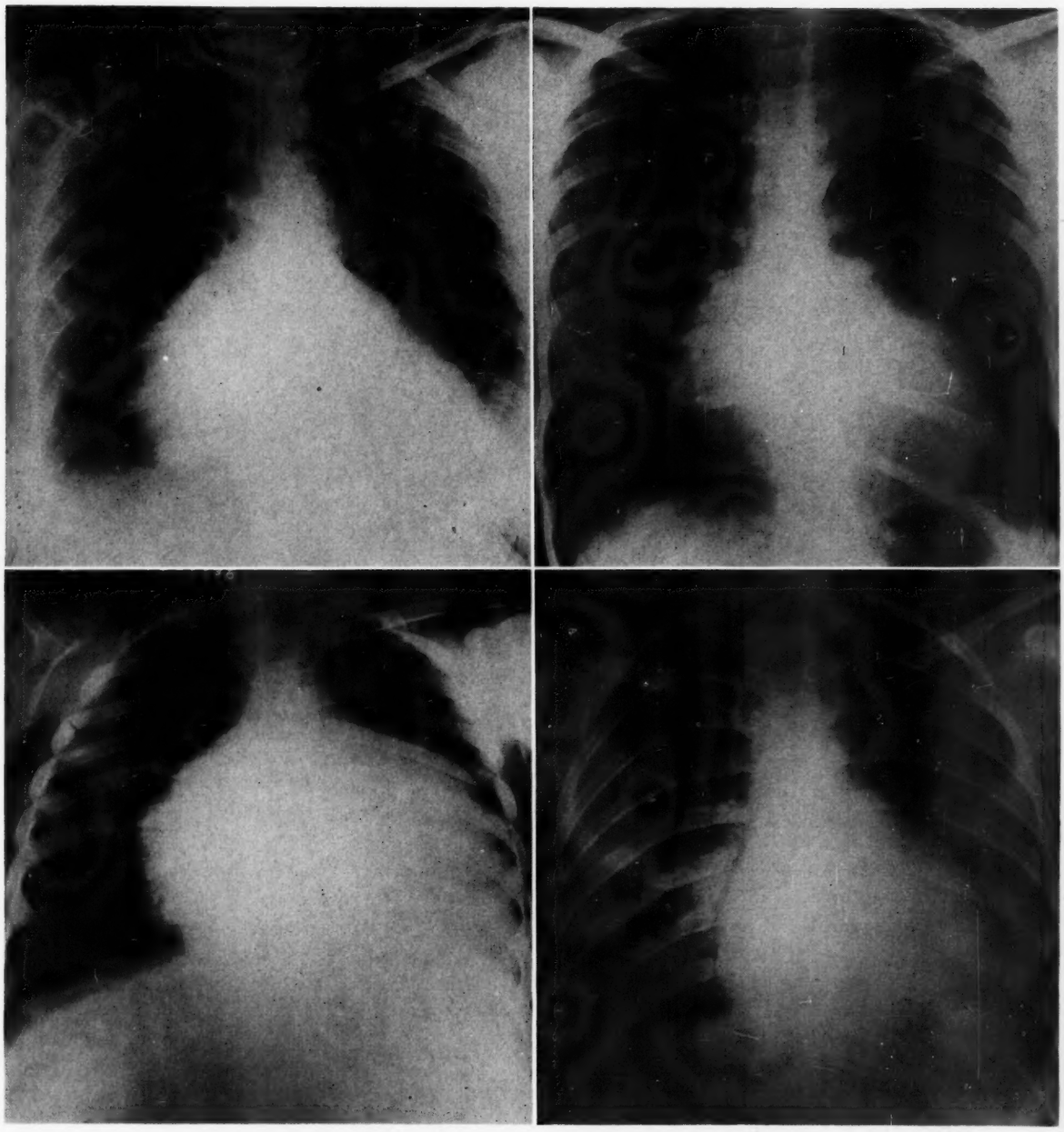


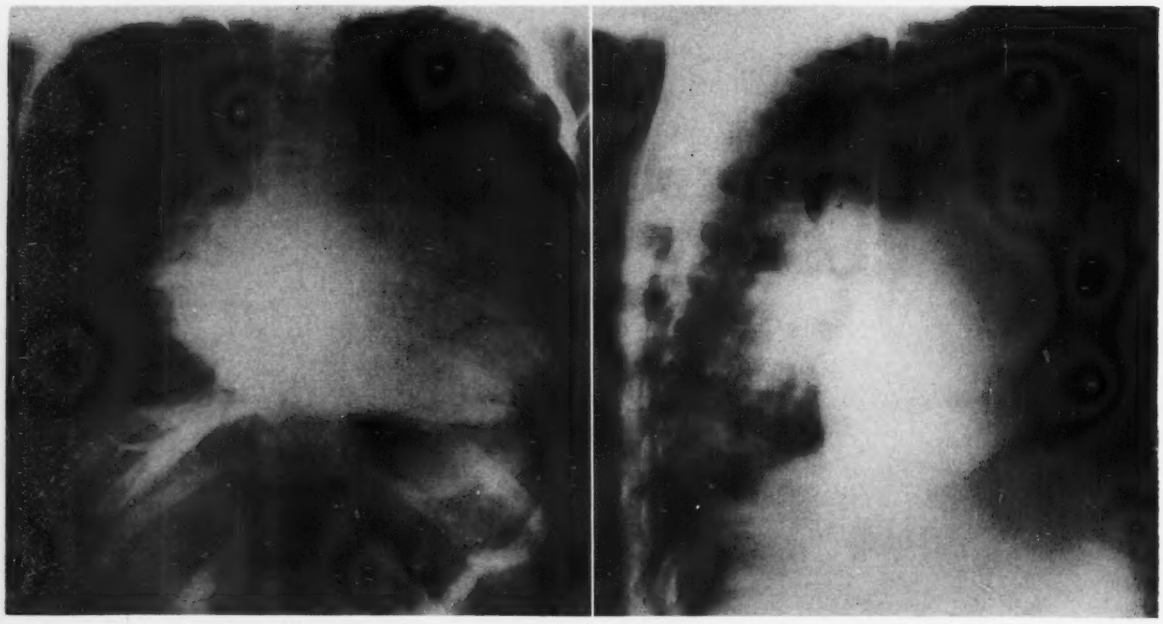
FIG. 2. Postero-anterior teleradiograms of four patients with Ebstein's disease. Upper: left, Case I; right, Case II. Lower: left, Case III; right, Case IV.

and below the annulus fibrosus. The whole of this chamber resembled dilated and hypertrophied right atrium. (Fig. 5.)

The tricuspid valve was grossly abnormal. An anterior leaflet was present but the medial and posterior leaflets consisted only of bands of fibrous tissue lying in the ventricular septum and the posterior wall of the heart. The tricuspid valve appeared grossly incompetent and four fingers passed with ease from the huge chamber above into the right ventricle proper. (Fig. 5.)

There was a patent foramen ovale one-half inch in diameter. The left atrium and the left ventricle were normal. The mitral, pulmonary and aortic valves were normal. There was no ventricular septal defect. The great vessels arose normally from the ventricles. There was no atheroma of the pulmonary artery. On histologic examination the small pulmonary vessels showed only intimal sclerosis but this was regarded as a normal age change.

CASE III. The findings were similar to those described in Case I except that there was no defect in the



3A 3B

FIG. 3. Anteroposterior and lateral angiocardiograms taken three seconds after the injection of the contrast medium in Case II (A) and Case III (B), showing huge right atrium.

TABLE IV

RESULTS OF CARDIAC CATHETERIZATION IN THREE PATIENTS WITH EBSTEIN'S DISEASE

Case	Blood Oxygen Saturation Per cent					Mean Blood Pressure in mm. Hg	
	Inferior Vena Cava	Right Atrium	Superior Vena Cava	Right Ventricle	Right Pulmonary Artery	Right Auricle	Right Pulmonary Artery
II	69.6	70	62	68	72	4	10
III	62.4	62	61.5	Not catheterized		14	Not catheterized
IV	65	53	....	Not catheterized		11	Not catheterized

interatrial septum. The insertion of the tricuspid valve was higher than in Case I. (Fig. 6.) A Chiari network was present in the right atrium. (Fig. 7.)

OBSERVATIONS

Symptomatology. All the patients in our series complained of breathlessness, which has been frequently reported by previous authors.[3,9,12,14,18] As dyspnoea may occur in any form of congenital heart disease it is in no way characteristic of the present anomaly. The other common symptom, occurring in three of the present group of patients, was palpitation which was due to attacks of paroxysmal tachycardia in two. Such attacks have been previously reported by Brown,[5] Tourniare et al.,[6] Engle et al.,[3] Graux and Merlen[7] and Broadbent et al.[8] and are very characteristic of Ebstein's disease.

Signs. The auscultatory signs found in Ebstein's disease are characteristic but not diagnostic of the anomaly since they are not sufficiently specific. Medd et al.,[4] reviewing twenty-seven cases reported since 1948 and describing the findings in another, noted that a systolic murmur was present in twenty of the twenty-six cases in which clinical details were available. They also found that a diastolic

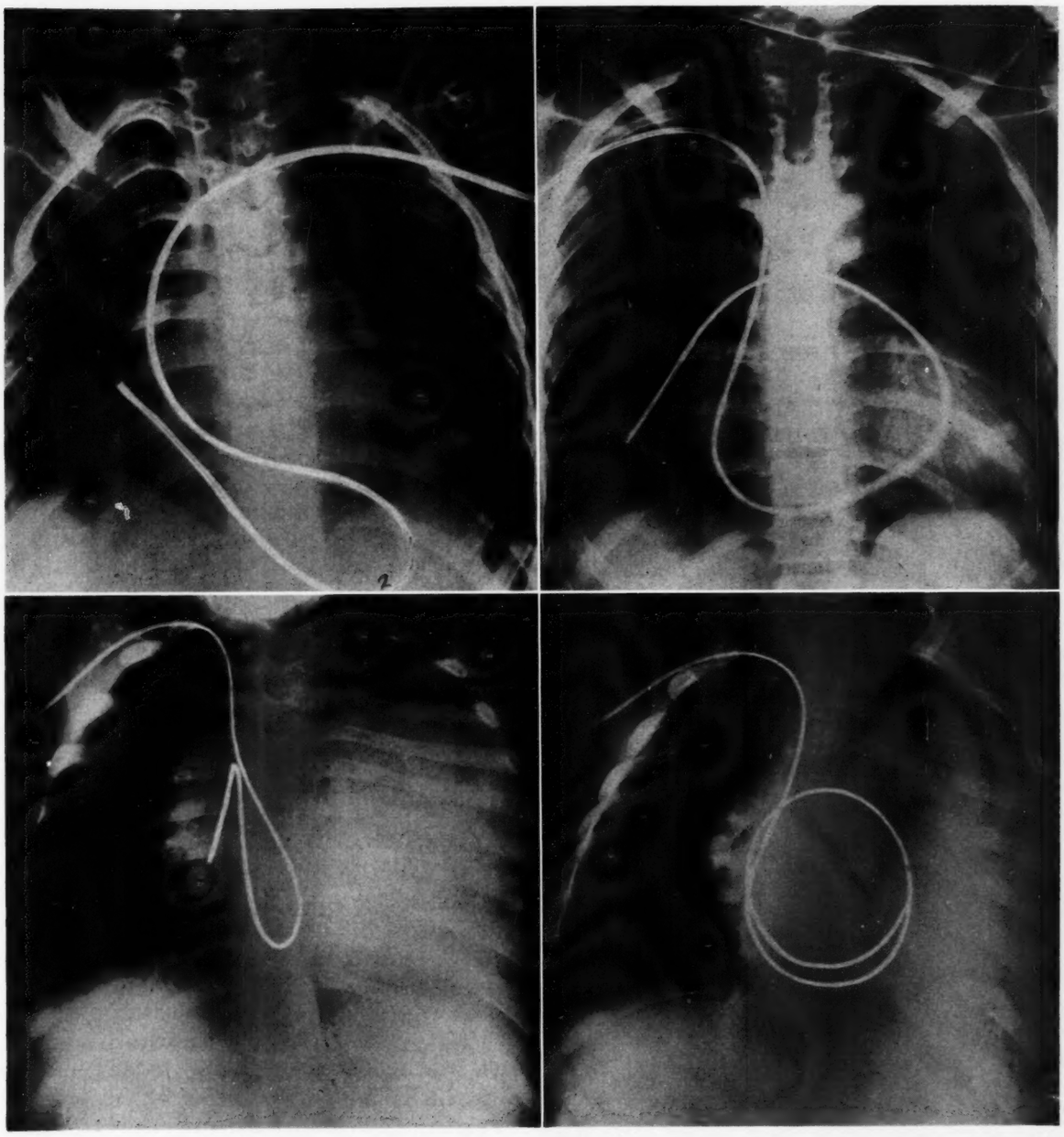


FIG. 4. Films taken at cardiac catheterization in Cases II, III and IV showing the cardiac catheter, coiled in huge right atrium in Cases III and IV and passing into the right pulmonary artery in Case II. Upper: left, Case IV; right, Case II. Lower: Case III.

murmur had been noted in thirteen of these cases and that a triple rhythm was present in sixteen of nineteen patients when a comment was made on this sign. These findings are in accord with the present series in which all the patients had soft praecordial systolic murmurs and apical protodiastolic triple rhythms, and one (Case II) had a widely split first heart sound and a soft rumbling apical diastolic murmur. From a phonocardiographic analysis of the heart sounds in their case, Medd et al.[4] found that the added sound present on auscultation occurred early in diastole and thought that it coincided with the opening of the tricuspid valve. They also noted that the phonocardiogram showed a fourth heart sound, which was also observed by Goodwin et al.[9] on the phonocardiograms of two patients with Ebstein's disease and con-

FIG. 5. Case I. Huge right atrium has been opened to show atrial septal defect (ASD) and tricuspid orifice (TO) guarded by malformed tricuspid valve.

FIG. 6. Case III. Heart has been opened to show huge right atrium (RA) with its Chiari network (CN), malformed tricuspid valve and small thick-walled functioning right ventricle (RV).

sidered by them to be due to contraction of the hypertrophied right atrium.

Central cyanosis is a common feature of Ebstein's disease and in the cases reviewed by Medd et al.[4] was present in seventeen of twenty-one cases in which information on this sign was available. However, the cases reported by Tourniere et al.,[6] van Lingen et al.[10] and the first, second and fourth cases of Blacket et al.[11] were acyanotic, while in the second case reported

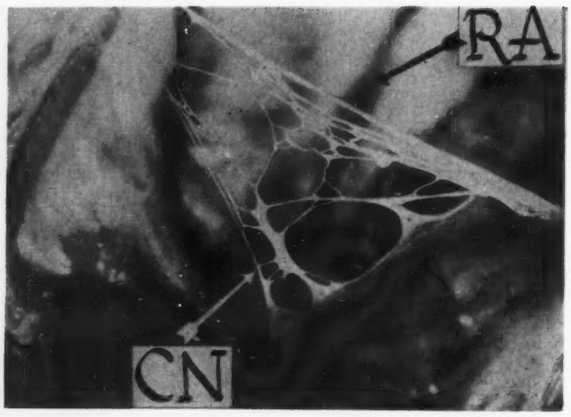


FIG. 7. Case III. Right atrium (RA) opened to show Chiari network (CN).

by Baker et al.[12] there was only peripheral cyanosis. In the present series Case IV had central cyanosis, Case II had peripheral cyanosis, Case III was acyanotic and Case I was acyanotic at rest and cyanotic during attacks of paroxysmal tachycardia. (Table I.) The development of

TABLE V
HAEMOGLOBIN AND HAEMATOCRIT VALUES IN FOUR PATIENTS WITH EBSTEIN'S DISEASE

Case	Haemoglobin (gm. %)	Haematocrit (%)
I	14.8	..
II	14.5	44
III	11.2	43
IV	18.2	54

central cyanosis in Ebstein's disease is probably due to an abnormally high right auricular pressure shunting venous blood through an atrial septal defect from the right to left atrium. An atrial septal defect was found at autopsy in Case I of the present series and also in the case reported by Engle et al.,[3] the first case of Baker et al.,[12] the first case of Goodwin et al.,[9] the case of Barger et al.[13] and the first case of Broadbent et al.[8] in which central cyanosis had been observed in life. In Case III of our series and in Blacket's[11] second case, in which central cyanosis did not develop in life, no atrial septal defect was present although at autopsy the tricuspid valve showed the typical deformity associated with Ebstein's disease.

The age of onset of cyanosis is variable. In our

Case IV and in the first case reported by Baker et al.[12] cyanosis was present at birth, in the first case reported by Goodwin et al.[9] cyanosis developed during adolescence and in our Case I it did not occur until middle age. (Table I.) Also in Case I in which the central cyanosis occurred only during attacks of paroxysmal tachycardia the rapid heart rate probably led to a rise in the right auricular pressure and a shunt of blood through the atrial septal defect from the right to the left atrium.

Clubbing of the fingers was present only in Case IV of our series, with the most marked degree of central cyanosis.

Since the cardinal feature of this anomaly is gross deformity of the tricuspid valve, it might be expected to be associated with clinical features of tricuspid incompetence. Although Ebstein[1] noted pulsation of the liver sixteen days before the death of his patient, there are no other reports of clinical evidence of tricuspid incompetence nor was there any evidence of this complication in the present series, even in the right auricular blood pressure records. Broadbent et al.[8] noted abnormal systolic venous waves in the right auricular blood pressure tracings of a patient with Ebstein's disease in cardiac failure. Baker et al.,[12] commenting on the absence of clinical signs of tricuspid incompetence, considered that the eustachian valve might protect the venae cavae from the effects of the tricuspid regurgitation which must be present. However, from an anatomic consideration of the size of the tricuspid orifice in Ebstein's disease such an explanation seems unlikely and the absence of signs of tricuspid incompetence is more probably due to an abnormally small regurgitant stream from the anatomically small right ventricle entering an abnormally large right atrium which acts as a buffer. Such a view is in accord with Yater and Shapiro[2] who also thought that an atrial septal defect allowing blood to escape into the left atrium in addition avoided a regurgitant effect in the systemic veins.

Ebstein's disease occurs in both sexes. The age range in the present series is nine to fifty-one years, but Blacket et al.[11] described a case in a male aged two and one-half years and Graux and Merlen[7] reported a case in a man aged seventy-two years. The disease evidently may be benign and compatible with longevity. Dulness on percussion to the right of the sternum was found in two of the four cases (Cases I and II) in the present series and was presumably due to the enlarged right auricle.

Electrocardiography. Electrocardiograms may be valuable in diagnosis since peaked P waves and right bundle branch block patterns frequently occur. Three of the four patients in the present series had such P waves (Table II, Fig. 1); these waves occurred in nineteen of the twenty-five cases of Ebstein's disease reviewed by Medd et al.[4] Peaked P waves are probably an electrocardiographic manifestation of the huge right atrium which is present in this disease. Right bundle branch block, either complete or incomplete, occurred in twenty of the twenty-five cases reviewed by Medd et al.[4] and was present in Cases I and II of our series. (Table II, Fig. 1.) The attacks of paroxysmal tachycardia characteristic of the condition may be recorded electrocardiographically, as in Case I. (Fig. 1.)

Radiology. Patients with Ebstein's disease have a characteristic radiologic appearance: moderate to marked over-all cardiac enlargement with increased prominence of the right border, due to the large right atrium. All the patients in the present series showed this characteristic globular cardiac silhouette which was rendered even more apparent by the diminished pulmonary vascularity which was present in Cases I, II and III. (Table III, Fig. 2.) Similar radiologic appearances have been reported with great frequency by other authors who have also noted on screening a large right atrium, diminished movement of the right ventricle and poor pulsation of the pulmonary artery.[3,8,9–12,14,18]

The radiologic appearance may suggest a pericardial effusion. Although Case III had in addition to the cardiac anomaly a tuberculous effusion, there is no evidence to suggest that a pericardial effusion usually contributes to the radiologic picture in Ebstein's disease.

Angiocardiography. Angiocardiography is a valuable investigation in the diagnosis of Ebstein's disease. In all four of our patients this technique demonstrated a large right atrium from which the contrast medium emptied slowly, and in Case IV the cavity of a small right ventricle was also outlined. (Fig. 3.) In one patient described by Soloff et al.[14] angiocardiograms showed a huge right atrium, an "auricularised" right ventricle and a small functioning right ventricle as distinct opacities. These observers thought that the non-opacified band separating the auricularised and functioning right ventricles was due to the misplaced

tricuspid valve and considered that this angiocardiographic sign was diagnostic of the anomaly. Goodwin et al.[9] noted this sign in their case but it was not seen in the angiocardiograms in the present series. In addition to outlining the abnormal chambers on the right side of the heart angiocardiography may demonstrate an atrial septal defect. Early filling of the left atrium occurred only in Case I of our series; this patient was found to have an atrial septal defect at autopsy. Although the other patient examined at autopsy (Case III) had no atrial septal defect, the absence of early filling of the left atrium on angiocardiography cannot exclude conclusively an atrial septal defect since such a defect was present in the first case of Goodwin et al.[9] in which there was no evidence of a shunt from right to left atrium. In the present series the pulmonary arteries were outlined by contrast medium only in Case III in which they appeared to be abnormally small. The poor filling of the pulmonary vessels was thought to be due to the delay of the dye in the right atrium, permitting it to be diluted before passing into the right ventricle.

Cardiac Catheterization. Experience has shown that cardiac catheterization is an investigation which carries considerable hazard in patients with Ebstein's disease. Cardiac arrhythmias are common and occurred in two patients in the present series during cardiac catheterization. Deaths during this investigation have been reported by Blacket et al.[11] and Campbell,[15] and death from bilateral gangrene of the lower legs and feet nine days after the investigation by Baker et al.[12] Cerebral embolism occurred in a patient of Burchell et al.[16] three weeks after cardiac catheterization. Campbell[15] thought that as the diagnosis could often be made on clinical grounds the investigation should not be carried out unless there were very special reasons for it.

In reported cases in which this investigation was carried out a high right auricular blood pressure had been demonstrated which, when the right ventricle and pulmonary arteries had been entered, was associated with normal right ventricular and pulmonary artery blood pressures. In the present series the right auricular mean blood pressures were 4, 14 and 11 mm. Hg (see Table IV) and in reported cases have varied between 25-13 mm. Hg[8] and 3 mm. Hg.[9] The right ventricle and pulmonary arteries were catheterized only in Case II and normal blood pressures were found. (Table IV.) Similar normal blood pressures were recorded in the right ventricle and the pulmonary arteries by patients reported by Tourniare et al.,[6] Mannheimer et al.,[17] van Lingen et al.,[10] Blacket et al.,[11] Broadbent et al.[8] and Henderson et al.,[18] while Broadbent et al.[8] found a slightly elevated pulmonary artery and right ventricular blood pressure (34/22) in their third case.

As pointed out by Medd et al.[4] the combination of a raised right auricular blood pressure and a normal right ventricular blood pressure occurs only in Ebstein's disease and tricuspid stenosis. In the latter condition there is an abnormal diastolic blood pressure gradient between the right auricle and ventricle, the diastolic blood pressure in the auricle being higher than in the ventricle.[19] No such abnormal gradient was found in Case II in the present series of patients with Ebstein's disease.

Probably the most important diagnostic feature at cardiac catheterization is the anatomic demonstration of an abnormally large right atrium. When the cardiac catheter enters the right atrium it coils in a large chamber from which it is extremely difficult to pass into the right ventricle and into the pulmonary arteries. (Fig. 4.) Manipulation of the catheter at this stage is very liable to produce paroxysms of tachycardia such as those noted in Cases III and IV of this series.

Blood gas analysis in the present series showed no evidence of intracardiac shunts and it is not justifiable to subject patients with this anomaly to cardiac catheterization to obtain intracardiac blood samples.

PATHOLOGY

The anatomic features of reported cases of Ebstein's disease have been surprisingly constant and are exemplified by the autopsy findings in the two cases in the present series. The tricuspid valve is displaced downward into the right ventricle so that the posterior and medial cusps arise directly from the wall of the right ventricle and the interventricular septum, respectively, and only part of the anterior cusp arises from the annulus fibrosus. The cusps are usually undifferentiated and appear as fibrous bands lying on the endocardium, rendering the valve incompetent.

The portion of the sinus of the right ventricle which lies immediately below the annulus fibrosus and above the abnormal origin of the

tricuspid valve is incorporated into the auricular cavity and functions as part of that chamber. Soloff et al.[14] termed this the "auricularised" ventricle to contrast it with the functioning right ventricle with thick myocardium lying beneath the tricuspid ring. The right atrium is usually dilated and hypertrophied and the functioning right ventricle has an abnormally small cavity and abnormally thick walls. The foramen ovale is frequently patent.

The size of these chambers varies with the degree of downward displacement of the tricuspid valve.

There is anatomical similarity between Ebstein's disease and other forms of congenital abnormality of the tricuspid valve described as Type Ia. tricuspid atresia by Edwards and Burchell[20] and it seems probable that tricuspid atresia and Ebstein's disease are manifestations to a different degree of the same abnormal developmental process.

DIFFERENTIAL DIAGNOSIS

Ebstein's disease can usually be differentiated from other forms of cyanotic and acyanotic congenital heart disease. Conditions such as atrial septal defect, ventricular septal defect or transposition of the great vessels, in which there is usually evidence of increased pulmonary blood flow, present little difficulty. The conditions most likely to be confused with this anomaly are those characterized by reduced pulmonary blood flow such as pulmonary stenosis with or without a septal defect, tricuspid atresia and Fallot's tetralogy. The acyanotic form of the anomaly is most likely to be confused with pulmonary stenosis and clinical differentiation from this condition may be impossible. A history of paroxysmal tachycardia, electrocardiographic evidence of right auricular hypertrophy and right bundle branch block, and radiologic and angiocardiographic demonstration of a large right atrium favour a diagnosis of Ebstein's disease. However, since gross enlargement of the right atrium is not incompatible with pulmonary stenosis, the final differentiation of Ebstein's disease from pulmonary stenosis with or without a septal defect may be dependent on cardiac catheterization. In patients with pulmonary stenosis there is an abnormal pressure gradient across the pulmonary valve while in patients with Ebstein's disease it is very difficult to pass the catheter out of the large right atrium but when this is achieved there is no evidence of pulmonary stenosis.

The cyanotic form of the anomaly must be differentiated from Fallot's tetralogy, tricuspid atresia and pulmonary stenosis with reversed flow through a septal defect. A history of paroxysmal tachycardia, the onset of cyanosis after infancy, the absence of squatting, electrocardiographic evidence of right bundle branch block and a grossly enlarged heart favour a diagnosis of Ebstein's disease rather than one of Fallot's tetralogy. The final differentiation of these two conditions is readily made on angiocardiographic examination; early filling of the ascending aorta from the right ventricle in patients with Fallot's tetralogy is in marked contrast to the slowly emptying enormous right atrium seen in patients with Ebstein's disease.

Tricuspid atresia may be closely mimicked by Ebstein's disease when there is a large atrial septal defect with a large blood flow from right to left atrium. Clinically it may be impossible to differentiate the two if there is a history of cyanosis from infancy. On radiologic examination a large globular heart shadow with great enlargement of the right atrium is more suggestive of Ebstein's disease than tricuspid atresia, usually accompanied by only moderate cardiac enlargement. On electrocardiographic examination peaked P waves may occur in both conditions and in tricuspid atresia there is characteristically left axis deviation with signs of left ventricular hypertrophy and no evidence of right bundle branch block. On angiocardiographic examination there is usually not the marked early filling of the left atrium in Ebstein's disease that is seen in patients with tricuspid atresia but when the atrial septal defect is large the left atrium may fill from the right atrium. The angiocardiograms in such cases are similar to those seen in tricuspid atresia but may differ from them in the delay in emptying of the right atrium, the absence of the triangular clear area in the position of the right ventricle, and occasionally in showing the displaced tricuspid valve regarded by Soloff et al.[14] as pathognomonic of Ebstein's disease.

The radiologic appearance of the heart in Ebstein's disease is similar to that of pericardial effusion and Engle et al.[3] have pointed out that the anomaly may be confused with rheumatic pericarditis. Although in Case 3 of the present series a small pericardial effusion was present, such effusions ordinarily are not the cause of the

characteristic globular-shaped heart on radiologic examination.

TREATMENT

Ebstein's disease is compatible with many years of active adult life and there is no place at present for surgical treatment. Thoracotomy is extremely hazardous since mechanical stimulation of the heart frequently precipitates cardiac arrhythmias which have been fatal in patients during exploratory operations.

Procaine amide and prostigmine were both used successfully to terminate paroxysmal attacks of tachycardia in patients in this series (Cases I and III). In Case I in the present series bouts of cardiac arrhythmia occurred in spite of oral therapy with quinidine and procaine amide. Terminally the attacks failed to respond to parenteral therapy with prostigmine and procaine amide.

SUMMARY

Four patients with Ebstein's disease are described and an account of the autopsy findings is given in two.

Breathlessness on exertion, cyanosis and palpitation were common symptoms. On physical examination there was a praecordial systolic murmur and a well marked triple rhythm at the apex in all four patients. Two patients were dull to percussion to the right of the sternum. Central cyanosis was present at rest in one and during attacks of paroxysmal tachycardia in another.

There was electrocardiographic evidence of right auricular hypertrophy in the form of peaked P waves in three and a right bundle branch block pattern in two.

On radiologic examination all the patients had an enlarged globular cardiac silhouette mainly due to the abnormal right atrium. Angiocardiography showed a huge right atrium in all cases and early filling of the left atrium in one case subsequently found to have a patent foramen ovale at autopsy.

Three of the four patients were investigated by cardiac catheterization and in each case the catheter coiled in a large right atrium. The right atrial pressure was raised in two; only in one was it possible to catheterize the pulmonary artery and in this instance the pressures were normal.

At autopsy the abnormalities characteristic of Ebstein's disease were found in both cases. A patent foramen ovale was present in only one of these. The pulmonary vessels were examined histologically in one case and showed changes normal for the age of the patients.

There is at present no indication for surgical treatment of this anomaly.

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The Mechanism of A-V Arrhythmias*

With an Electronic Analogue of the Human A-V Node

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In atrioventricular arrhythmias the spread of activation from the atria to the ventricles is disturbed. Examples of this include fixed P-R interval prolongation, Wenckebach's phenomenon, A-V dissociation with or without interference, various types of nodal and reciprocal rhythms, and incomplete and complete heart block. The bizarre and often quite intricate relationships between the atrial and ventricular rhythms in these disorders have intrigued clinicians for years. However, the theories that have been offered in the past to explain A-V arrhythmias are difficult to reconcile with modern excitation theory. This is not surprising when it is realized that even the conduction delay between atria and ventricles in normal sinus rhythm has never been satisfactorily explained. However, there are two aspects of these arrhythmias which have generally escaped attention in the past and suggest an entirely new approach to the mechanisms of the A-V arrhythmias. Both are well illustrated by the A-V arrhythmias of acute rheumatic fever (A.R.F.).

First, while the incidence of P-R prolongation, Wenckebach periods, A-V dissociation and nodal rhythm is much higher in A.R.F. than in normal subjects or in other diseases, incomplete and complete heart block are exceedingly rare in this disease. Previous explanations of P-R prolongation and Wenckebach periods have attributed them to varying degrees of delay in conduction along the fibres of the A-V node. However, the fact that higher degrees of conduction failure do not occur in A.R.F. suggests that conduction delay is not the cause of these arrhythmias, and the mechanism responsible for incomplete and complete heart block must be different from that which produces the other A-V arrhythmias. For this reason in the present discussion the term "A-V arrhythmias" will refer to the latter disorders while the term "heart block" will be used only for incomplete and complete heart block.

Second, in A.R.F. P-R prolongation, Wenckebach periods and A-V dissociation are often found in the same subject. In fact, as will be shown, a patient with P-R prolongation due to A.R.F. can often be caused at will to exhibit either Wenckebach periods or A-V dissociation. This suggests that the A-V arrhythmias are due to a single type of A-V node defect with fixed P-R prolongation representing a stable operation of the defect, while Wenckebach periods and A-V dissociation represent unstable forms of operation of the defect.

This interrelationship among the A-V arrhythmias and the specific time constants of Wenckebach periods and A-V dissociation closely resembles the arrhythmic behavior produced when two electronic oscillators of easily disturbed stability are coupled. In this instance one oscillator would represent the P impulse coming into the A-V node from the atria; the other oscillator would represent rhythmic potential variations within the A-V node which are usually subthreshold but may on occasion become the effective pacemaker of the ventricles, as in A-V dissociation.

Of course, the human A-V node is inaccessible to direct study. Accordingly, the existence of such subthreshold nodal activity in A.R.F. cannot be directly verified and can only be inferred from the clinical characteristics of the A-V arrhythmias. However, in recent years studies of other neuromuscular junctional organs and of isolated Purkinje tissue have shown that non-propagated and oscillating potentials may play a part in normal biological excitation. By incorporating these properties into the design of

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a circuit of coupled oscillators an electronic analogue for the A-V node can be built. On graded change of but a single parameter of this analogue, the "normal" P-R interval is changed to fixed P-R prolongation, then the instrument goes into Wenckebach periods and A-V dissociation that duplicate in detail those seen in A.R.F.

This analogue leads to a hypothesis for the mechanisms of A-V arrhythmias which is on sounder clinical and electrophysiologic grounds than previous hypotheses. In addition it explains a number of clinical aspects of the A-V arrhythmias which have been perplexing in the past. Finally, it demonstrates that the A-V node may have excitation properties which are similar to those encountered in other neuromuscular systems. This provides a rationale for applying the wealth of pharmacologic and physiologic information that has accumulated in recent years regarding neuromuscular conduction to problems of cardiac rhythmicity and irritability.

CLINICAL ASPECTS OF THE A-V ARRHYTHMIAS

Prolongation of the P-R interval occurs in as high as 80 per cent of cases of A.R.F.[1–3] and, with atropinization and other technics, can be shown to have an even higher incidence.[3–7] Usually this P-R prolongation is relatively constant for a given patient and lasts for weeks or even months, gradually returning to normal. Wenckebach periods, A-V dissociation and nodal rhythm also occur not infrequently in A.R.F.[7–13] However, they are always short-lived and perhaps that is why they have not been identified in as high a percentage of cases. On the other hand, they have never been described in A.R.F. without preceding or following periods of fixed P-R prolongation.

Even more persuasive clinical evidence of the interrelationship of these arrhythmias is the demonstration that a patient with P-R interval prolongation due to A.R.F. can be caused transiently to develop one or more of the other arrhythmias at will. For example, if a patient with P-R prolongation due to A.R.F. is passively tilted to 60 degrees for five minutes, on lowering to the horizontal position transient A-V dissociation or Wenckebach periods will appear. (Fig. 1.) This has been found repeatedly in four of five consecutive patients with P-R prolongation due to A.R.F., in one of whom transient A-V dissociation was also recorded following a paroxysm of coughing. Such transient bursts of arrhythmia in patients with P-R prolongation due to A.R.F. have been reported following breath-holding and other maneuvers.[4,10,14,15]

This type of lability of A-V conduction is not seen in certain other conditions associated with P-R prolongation, which suggests that there may be more than one mechanism for P-R prolongation. In four cases of P-R prolongation due to digitalis effects and three cases of P-R prolongation due to arteriosclerotic heart disease no change in A-V conduction was produced by passive tilting. Also, while mild exercise does not alter the P-R interval in A.R.F.[3,15,16] it will increase the P-R delay and produce 2:1 or higher degrees of block in patients with P-R prolongation due to digitalis, arteriosclerotic heart disease or myocardial infarction.[15–18] Still another mechanism for P-R prolongation is encountered in certain normal young subjects who when recumbent show P-R prolongation or Wenckebach periods which vanish on mild exercise, passive standing or even during deep inspirations, a type of normalization which is not seen in the arrhythmias of A.R.F.[20–30] Atropine regularly restores normal rhythm in these subjects, as it does in A.R.F., but only infrequently restores normal conduction in subjects with P-R prolongation due to digitalis or arteriosclerotic heart disease.

On the other hand, 2:1 and higher degrees of block, including complete heart block, are exceedingly rare among cases of A.R.F., in contrast to other causes of P-R prolongation.[1,31,32] In one series of 6,000 cases of A.R.F. only one case of complete heart block was encountered.[33] Of thirteen cases of complete heart block reported in association with A.R.F. one patient was sixty-four years of age,[34] another had coexisting auricular fibrillation,[35] one had frank aortic insufficiency,[36] and one had a single attack of transient complete heart block with neither preceding nor following P-R prolongation;[37] it is possible that additional organic factors were responsible for the complete heart block in these cases. Nine cases of complete heart block have been reported in patients with A.R.F. and hyperthyroidism, and the author has seen another; but since at least eighteen cases of complete heart block have been recorded as associated with hyperthyroidism alone, it is likely that the metabolic disorder contributed to the development of complete heart block in these cases.[38–43] In addition, in a few cases complete heart block has been noted to occur in young patients with upper respiratory infec-

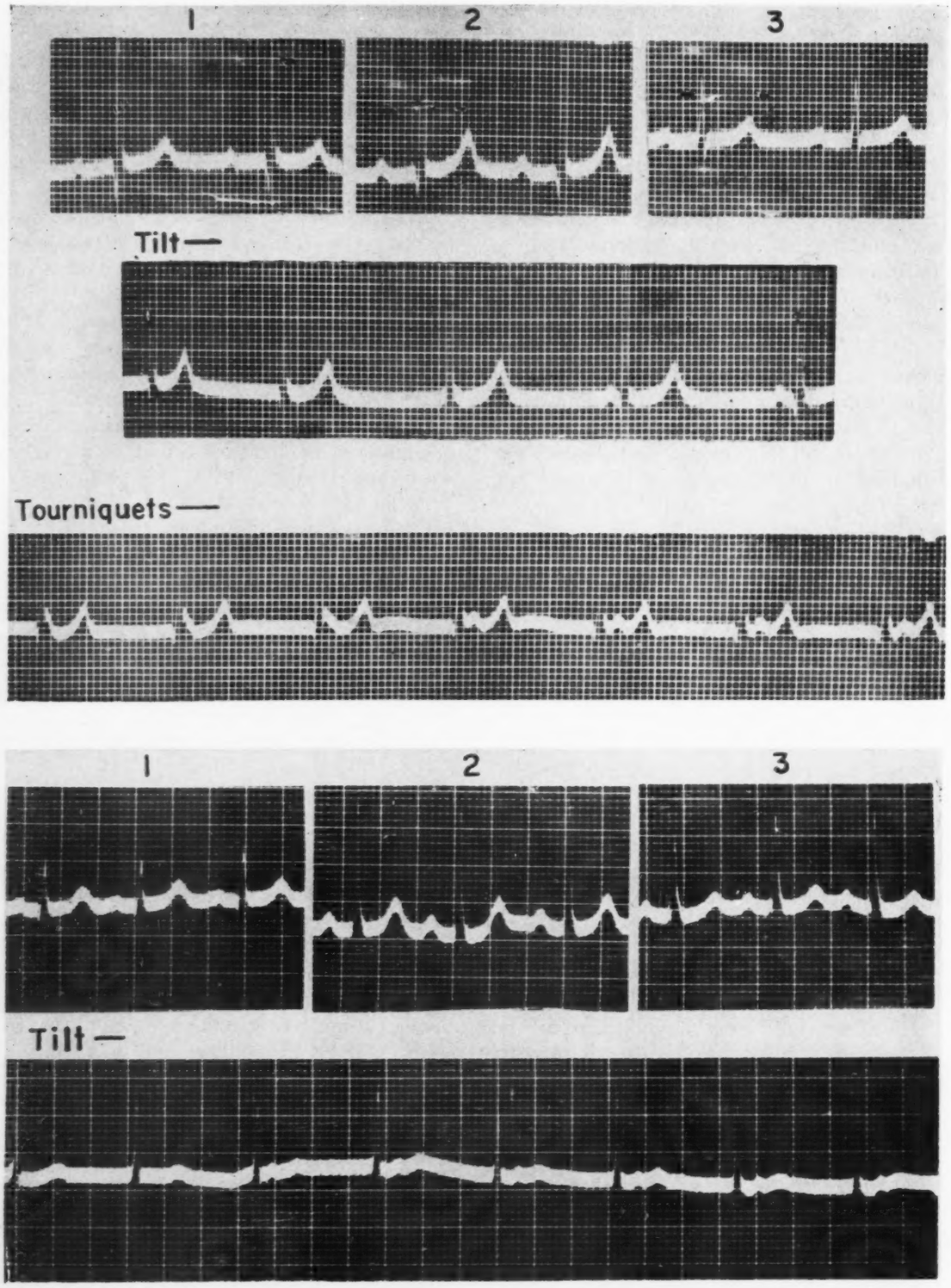

FIG. 1. Above, transient A-V dissociation following tilt and release of venous tourniquets (which simulates the effects of tilting) in a twenty-two year old male with acute rheumatic fever. Below, transient A-V dissociation following tilt in an eighteen year old male recovering from acute rheumatic fever; the P-R interval was then normal.

tions but without other stigmas of A.R.F.[44,45] This leaves only three cases of probable complete heart block attributable to A.R.F. and in these cases few clinical data are given.[1,33,46]

To complete the picture of the relationship between P-R prolongation and complete heart block, not only does P-R prolongation of A.R.F. rarely lead to complete heart block but also in those diseases in which complete heart block does occur, preceding P-R prolongation plays an inconstant role. For example, when complete heart block develops in diphtheritic myocarditis, carotid sinus hypersensitivity or acute myocardial infarction, fixed P-R prolongation rarely precedes or follows it.[47–50] On the other hand, when complete heart block develops in arteriosclerotic heart disease, aortic valve disease or following digitalis intoxication, it is usually preceded by an interval of P-R prolongation.[51,52]

There is another way in which the A-V conduction defect of A.R.F. differs from that seen in other states. In A.R.F. the gradual increase in the P-R interval leading to the dropped beat in Wenckebach periods follows a fixed pattern in a given cycle and tends to be the same from cycle to cycle and from case to case. Indeed, it has been possible to construct an equation, expressing the exponential decrease in P-R increment leading to the dropped beat, which will fit most cases of A.R.F. with Wenckebach periods.[18] On the other hand, the Wenckebach periods which occur with digitalis intoxication or following myocardial infarction follow quite different patterns of P-R prolongation and vary from cycle to cycle.[18,53]

In summary, the A-V rhythm disturbance of A.R.F. appears to be unique among causes of A-V conduction disorders. It is characterized by an abnormality which in its stable form presents P-R prolongation but is capable of unstable variations in performance which manifest themselves as A-V dissociation, Wenckebach periods and nodal rhythm but rarely as complete failure of A-V conduction. It is due to a functional rather than structural alteration in the A-V node because it is uniformly corrected by intravenous atropinization. On the other hand, this responsiveness to atropine probably does not represent increased central vagus activity for there are no other manifestations of vagus hyperactivity and attempts to reproduce a constant P-R prolongation or the other A-V node arrhythmias by graded vagus stimulation or by the administration of cholinergic drugs alone have never been successful.[54–56] Only two methods have been described for reproducing these arrhythmias in the experimental animal. In one method graded stimulation of the vagus nerve combined with carefully timed administration of adrenalin® produced reasonably fixed P-R prolongation.[57] In the other, graded stimulation of the vagus in an explanted nonperfused heart produced Wenckebach periods; but when the heart was perfused with Ringer's solution, only 2:1 and higher forms of block could be produced.[58] These two experiments suggest that an A-V nodal abnormality is a necessary part of the mechanism for the production of the arrhythmias. This is supported by clinical evidence for, as has been shown, an intrinsic characteristic of the A-V conduction defect in A.R.F. is its propensity to develop into A-V dissociation. It is likely, then, that enhanced nodal rhythmicity is a part of the basic A-V nodal abnormality seen in A.R.F.

ELECTRONIC ANALOGUE FOR THE A-V NODE

The oscillating nature of the heart beat has intrigued physiologists and physicists for many years and several attempts have been made to construct electrical circuit analogues to simulate cardiac rhythmicity and arrhythmicity. It is of interest that recognition of the fact that the heart beat is not sinusoidal but consists of periodic bursts of electrical activity separated by relatively long rest or "relaxation" periods was part of the first mathematical formulation of what is now a basic concept in electrical engineering and standard electronic equipment, the "relaxation oscillator."[59] Although 2:1 and other types of incomplete block could be simulated by these circuits, none were capable of producing Wenckebach periods. Later, Bethe constructed a circuit consisting of two coupled oscillators, one to represent the P impulse and the other some subthreshold oscillation elsewhere in the conduction system which produced periodic dropped beats. However, the intervening P-R intervals did not "grow" in the manner of Wenckebach periods and fixed P-R prolongation was not a stable operation of the circuit.[60]

Nevertheless, the possibility that subthreshold oscillations in the A-V node may play a basic role in normal and abnormal A-V nodal function is a reasonable one. There is clinical evidence of nodal rhythmicity in A-V dissociation, nodal rhythms, nodal escapes, nodal extrasystoles and complete heart block in each of which the

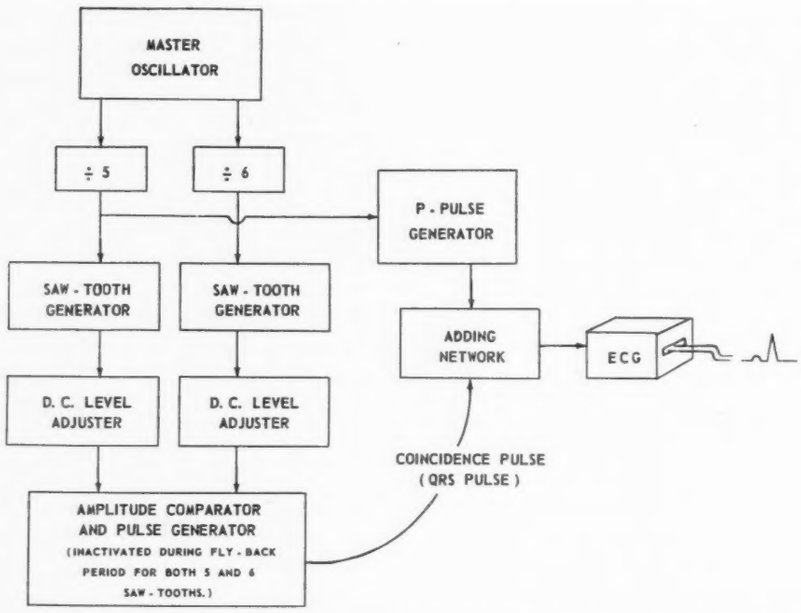
MASTER OSCILLATOR
÷ 5
÷ 6
P - PULSE GENERATOR
SAW - TOOTH GENERATOR
SAW - TOOTH GENERATOR
ADDING NETWORK
ECG
D. C. LEVEL ADJUSTER
D. C. LEVEL ADJUSTER
COINCIDENCE PULSE (QRS PULSE)
AMPLITUDE COMPARATOR AND PULSE GENERATOR (INACTIVATED DURING FLY - BACK PERIOD FOR BOTH 5 AND 6 SAW - TOOTHS.)

FIG. 2. Block diagram of electronic circuit which will simulate normal and abnormal A-V conduction.

A-V node may become the pacemaker of the ventricles. Also, in the experiments mentioned earlier in which P-R prolongation was produced, adrenalin administration was necessary, and this drug is known to enhance nodal rhythmicity.[3] Finally, it has long been known that excised strips of Purkinje and myocardial tissue generate rhythmic electrical potentials which often are non-propagated.[61–63]

However, a coupling of two oscillators cannot produce the counterpart of P-R prolongation or Wenckebach periods unless the pulses from the two oscillators can be shaped to have certain specific time-amplitude characteristics. That the oscillation in the A-V node might on integration have the necessary "saw-tooth" form is a reasonable presumption from the information available as to the shape of the spontaneous rhythmic potentials recorded from Purkinje tissue.[63] However, the incoming P impulse is a brief action potential and does not have the proper duration to produce these arrhythmias when coupled with the nodal oscillation. A justification must be found for shaping this impulse into a longer and differently shaped signal before an A-V analogue can be made which will reproduce these arrhythmias.

In recent years it has been demonstrated and generally accepted that in the motor end-plate of skeletal muscle and perhaps at other neuromuscular junctions the incoming nerve impulse sets up a local non-propagated potential which has slower time constants than a nerve action potential and plays a part in generating the impulse propagated along the membrane of the muscle fibres.[64–66] If the A-V node should have this property of the motor end-plate, the construction of an electronic analogue which will exactly duplicate the rhythmic aberrations seen in A.R.F. becomes quite simple. A block diagram for such an analogue is shown in Figure 2. The pulses from two oscillators of randomly different rate are appropriately shaped and fed into an amplitude comparator. When the voltages of the two pulses coincide, a pulse is sent out which writes a "QRS complex." The slower of the two oscillators is also fed directly into the electrocardiographic galvanometer to write a "P wave." In this way P and QRS complexes are recorded in sequences which reflect the differences in pulse timing and pulse shape of the two oscillators.

The electrical events which take place in the analogue are shown in Figure 3. These events may indicate in a very general and schematic way the events which take place in the A-V node in A.R.F. The "P" pulses from the slower oscillator are indicated by the small vertical bars in each set of curves. When this pulse arrives in the shaping circuit of the analogue it is given an S-shape, as shown in the diagram. This is analogous to the non-propagated potential

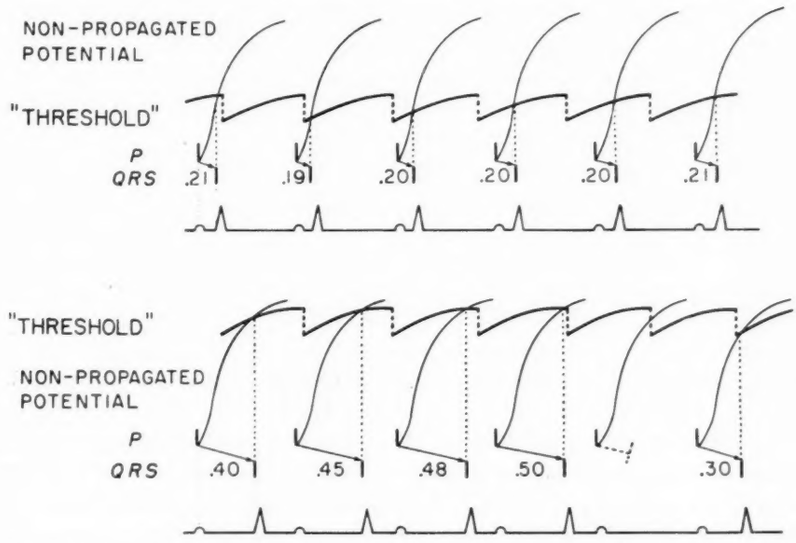

FIG. 3. Electrical events in the electronic analogue for the production of normal P-R interval above and Wenckebach periods below. See text for details.

which the P impulse generates on arriving in the A-V node. The slower oscillator of the analogue represents subthreshold nodal oscillation in the A-V node. It is given a saw-tooth form and its level of potential can be raised or lowered in the analogue. How the non-propagated potential and the nodal oscillation interact in the A-V node to reach the threshold of activation is not known. If they summate, construction of the analogue is greatly simplified for under these circumstances it is possible to consider the saw-tooth pulse in the diagram as "threshold" oscillating in response to the nodal potentials. When the two pulses reach the same voltage in the amplitude comparator and send out a QRS pulse, this is analogous to the nodal oscillation plus the non-propagated potential reaching the threshold of activation.

In the examples in Figure 3 the ratio of the rate of the "P" oscillator to that of the "threshold" oscillator is 5:6. The upper set of curves demonstrates the performance of the analogue when the threshold is relatively low. It can be seen that at these levels the slope of the S-curve is quite steep and therefore, in spite of the difference in rate, relatively constant P-R intervals of normal duration are produced. As the level of the threshold is raised the P-R interval becomes longer but is still fixed. At still higher levels, shown in the lower set of curves, the shape of the S-curve is such that now the analogue produces P-R intervals which increase by exponentially diminishing amounts, with every sixth beat a "dropped beat." This exactly duplicates Wenckebach's phenomenon as seen in A.R.F.[18] Then, when the amplitude of oscillations of threshold is increased at any mean level, the faster oscillator will tend to "run free." This is analogous to greater enhancement of nodal rhythmicity producing A-V dissociation. Should retrograde conduction out of the A-V node be possible, this enhanced nodal rhythmicity will produce nodal rhythm. In summary, the analogue progresses from "normal" P-R intervals through fixed P-R prolongation into Wenckebach periods and A-V dissociation as the amplitude or mean level of the faster oscillator is changed.

The extent to which the electrical events taking place within the analogue resemble known events in neuromuscular excitation deserves comment in certain regards. First, the durations of the S-pulse and the saw-tooth oscillation are reasonably close to the durations of non-propagated potentials in the motor end-plate and the spontaneous oscillations which have been described in Purkinje tissue. However, the particular shapes which are given to these pulses in the analogue were selected in order to make the analogue produce the desired arrhythmias and do not resemble the contours of potentials which have been recorded in these tissues. They more closely resemble curves of integration than they do action potentials. However, all studies of excitation show that it is the instantaneous level of the potential and not its integrated value that is the effective stimulus for excitation.

This is partly because of the conventions that are used in recording and interpreting excitation events. It does not rule out the possibility that under certain circumstances the integrated effects of voltage, or an equivalent of it, may be an adequate stimulus. Thus direct current, S-shaped curves of the duration used here have been shown to be an effective stimulus for excitation of Purkinje tissue;[67] also, a condenser-like effect of voltage accumulation has been shown to play a part in the end-plate of the electrical organ of the torpedo fish although with shorter time constants than in the analogue.[68] These curves would also fit the concept of accumulation of some chemical equivalent of voltage at a particular region of the A-V node, similar to that seen when excitation is artificially produced by injecting acetyl choline.[68]

A second aspect of the analogue which deserves mention is the requirement that the oscillations of "threshold" and the non-propagated potential be inactivated during their "fly-back" period, the phase of rapid change of voltage for each oscillation. This is not meant to suggest that physiologic threshold is periodically inactivated. It will be remembered that "threshold" in the analogue is the resultant effect of nodal rhythmicity on the threshold of activation. It is of interest that the envelope of non-propagated potentials recorded from Purkinje tissue resembles saw-tooth oscillations and there is a period of non-responsiveness at the end of each saw-tooth.[62] Perhaps this is true of nodal oscillations as well. In any case, inactivation by virtue of refractoriness or accommodation is a familiar neurophysiologic property and perhaps a property of the A-V node as well. In electronic systems it is common for an element to be inactive when voltage is rapidly changing and this is used in constructing the analogue.

Third, liberties have been taken with the interrelationship among nodal rhythmicity, the non-propagated event, and threshold in order to keep the design of the analogue simple. Certainly, the excitation events in the A-V node are more complex and inconstant than shown here. The analogue schematizes these events, indicating that variations of three general properties of neuromuscular transmission will explain normal and abnormal A-V node function. For example, the A-V arrhythmias of A.R.F. can be explained in terms of enhanced nodal rhythmicity and an elevated threshold of excitation. On the other hand, in the normal subjects described earlier with P-R prolongation when recumbent, an elevation of threshold is perhaps the sole defect. Vagus effects are in part responsible for the elevation of threshold in these cases, since atropine eliminates the P-R prolongation. Standing also normalizes the P-R interval in these subjects and it is well known that this maneuver produces an inhibition of vagus effects.[69] The reverse of this is also seen, namely, excessive inhibition of vagus effects with, in effect, threshold so lowered that normal nodal rhythmicity is released. This is observed in certain normal subjects who on deep respiration or mild exercise develop A-V dissociation or Wenckebach periods with no prior P-R prolongation.[14,20,29] It is also frequently seen transiently immediately after the administration of atropine in normal subjects.[14,70,71] These examples illustrate that the difference between normal and abnormal A-V node function is one of degree and due to physiologic rather than structural alterations of the node, as had previously been thought.

MECHANISM OF A-V ARRHYTHMIAS IN A.R.F.

When two oscillators of different rates are coupled, they tend to "pull in"; that is, the less stable oscillator adopts the rate of the more stable oscillator or some harmonic of it. Physicists have long recognized this as a basic property of electrical oscillators and it proves to be a property of heart rhythmicity as well. For example, when two frogs' hearts beating at different rates are placed side by side they promptly begin to beat synchronously.[72] Also, it has been shown that when subthreshold rhythmic shocks are applied to the frog heart the heart gradually adopts the same rate as that of the subthreshold stimulator.[73] A similar although less obvious synchrony takes place clinically in complete heart block. When the distribution of P waves relative to the location of QRS complexes is plotted from a long tracing in such a patient the P waves are not distributed randomly, as one might expect, but tend to cluster near the QRS complexes.[74] Perhaps this accounts for the slight irregularity in both auricular and ventricular rhythm in complete heart block. An even more striking synchrony occurs in certain cases of A-V dissociation, with all P waves adjacent to or superimposing the QRS complexes; this has been frequently described in the literature and an example is shown in Figure 4.

It is therefore reasonable to assume that in

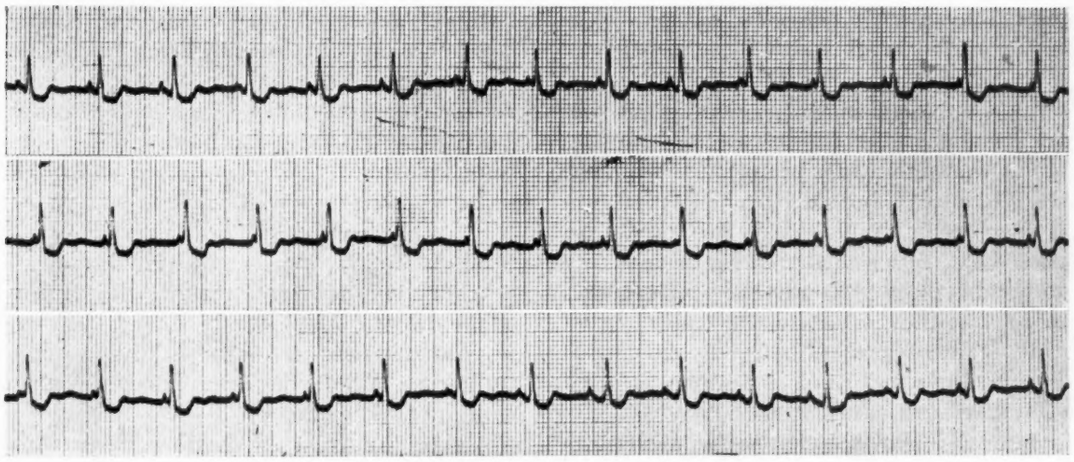

FIG. 4. Continuous tracing of lead II during A-V dissociation. Note that the ventricular and atrial rates are nearly the same with P and QRS complexes tending to cluster together.

the A-V node there is a tendency for the P oscillator and the subthreshold nodal oscillator to "pull in" as a stable form of operation of the node. This accounts for several features of the A-V arrhythmias which have been perplexing in the past. For example, if in the lower set of curves of Figure 3 the P oscillator and the nodal oscillator should have identical rates, the S-shaped curve of the non-propagated potential will cross threshold at exactly the same interval after the arrival of the P pulse for each beat. Thus when the two oscillators "pull in" a constant P-R interval is produced and the length of the P-R interval in a given case depends upon how high the threshold is. With a low threshold the stable operation of the analogue produces a fixed P-R interval of .20 seconds; with a high threshold it produces a constant P-R interval of as much as .50 seconds.

Previous theories of the A-V node mechanisms have been unable to account for either the stability of the P-R prolongation or the often striking degrees of P-R prolongation seen in A.R.F. In these theories the P-R prolongation is attributed to slowed conduction of the P impulse along the fibres of the A-V node. However, a process which can slow conduction without blocking requires such carefully graded control that it can scarcely be called "stable," and it is difficult to conceive of this same degree of slowing occurring in such a large per cent of cases of A.R.F. without ever going into higher degrees of block. Also, for a membrane to conduct a pulse so slowly that it takes .30 seconds or more to traverse without decrement a region which perhaps is only 1 or 2 mm. in length has no parallel elsewhere in electrophysiology.[67] On the other hand, if the A-V node is viewed as a system of coupled oscillators with a tendency to "pull in" and intermediated by a non-propagated potential, the stability and the extent of P-R prolongation are readily explained in terms which are consistent with present day excitation theory.

Then, when some pharmacologic or hemodynamic event slows the P rate in the presence of P-R prolongation, the two oscillators will lose their synchrony and Wenckebach periods will result, as shown in the lower set of curves. If the P slowing should be great, the nodal oscillator will run free, producing A-V dissociation as was observed when subjects with P-R prolongation due to A.R.F. were tilted. These arrhythmias will tend to be transient because the oscillators will "pull in," thus restoring the fixed P-R prolongation at the new rate.

Theoretically, if the two oscillators in the analogue should lose their synchrony by acceleration rather than by slowing of the P rate a "reverse" Wenckebach period should be produced, with the P-R interval progressively shortening before each "dropped beat." This arrhythmia has never been seen clinically and it does not occur in the analogue. The reason why the analogue does not produce it is because of a curious property of coupled oscillators: they do not become asynchronous as readily on accelerating one of them as they do on slowing one of them. "Pull in" is more readily maintained in an accelerating system than in a decelerating system. Whether this is also true of cardiac "pull in" is not known. In any case, when the P rate is

accelerated by exercise in a patient with P-R prolongation due to A.R.F., the P-R interval may remain unchanged or will become normal. Perhaps this normalization is due to the fact that exercise inhibits vagus effects, exerting an effect like atropine which also is known to restore the normal P-R interval in A.R.F. When the threshold is low, asynchrony of the two oscillators does not produce significant variations in the P-R interval in either the analogue or the human heart. This is illustrated by the upper set of curves in Figure 4 and explains why slowing of the P rate does not usually produce an A-V arrhythmia in normal subjects.

The most widely held theory of the mechanism of Wenckebach periods has been a morphologic one: it is presumed that successive P pulses leave progressively longer pathways of relative refractoriness within the A-V node so that each successive P pulse takes longer to traverse the node until one fails to traverse it and a "dropped beat" is produced. Such a theory explains the progressively longer P-R intervals but does not explain the mathematically precise nature of this progressive lengthening, with each P-R interval longer by an exponentially dwindling amount, or the fact that this pattern is nearly exactly duplicated in the majority of cases of Wenckebach periods in A.R.F. The precisely exponential nature of the P-R interval growth in Wenckebach's phenomenon in A.R.F. is itself strong evidence that the arrhythmia is related to some form of harmonic or resonant electrical behavior such as produced by coupled oscillators.

Not uncommonly, a patient with fixed P-R prolongation will exhibit a brief period of Wenckebach phenomenon, and the P-R interval of the last conducted beat will be shorter than the P-R interval before or after the Wenckebach episode.[18] This has been difficult to explain in previous theories because it has been generally assumed that Wenckebach periods are due to a more severe degree of A-V conduction abnormality than fixed P-R prolongation. However, it can be seen from the diagram that the two oscillators may pull apart and produce Wenckebach periods with the same progressive lengthening of the P-R interval at any degree of fixed P-R prolongation from .30 to .50 seconds. In short, the behavior of the analogue indicates that the lengths of the P-R intervals in the Wenckebach period are unrelated to the degree of P-R prolongation which preceded it. To this extent it is inaccurate to call Wenckebach periods "second degree heart block" and fixed P-R prolongation "first degree heart block," as has been customary in the past; they may not reflect different degrees of A-V conduction abnormality but rather different manifestations of the same abnormality.

In summary, it is suggested that in A.R.F. there is an elevated threshold in the A-V node in addition to enhanced nodal rhythmicity; that when under these circumstances the P rate and the nodal rate "pull in," fixed P-R prolongation is produced; and that when the two oscillators pull apart Wenckebach periods or A-V dissociation are produced.

In the analogue, the number of beats making up a Wenckebach period is a function of the ratio of the P rate to the nodal rate. For example, when the P-to-nodal rate ratio is 5:6, as in the diagram, there will be five conducted beats and the sixth will be a "dropped beat." In most instances of Wenckebach periods occurring in A.R.F. the fourth or the fifth beat is the "dropped beat."[18] This means that the majority of these patients have 3:4 or 4:5 P-to-nodal rate ratios. The reason why larger ratios are not commonly seen in A.R.F. is perhaps due to the circumstance that when the P rate differs markedly from the nodal rate, A-V dissociation usually appears. When the P rate is known, it is possible to calculate the nodal rate by counting the number of beats making up the Wenckebach cycle. At average heart rates with every fourth or fifth beat a dropped beat, the nodal rate must be in the neighborhood of 100 per minute, which is close to the ventricular rate seen in many instances of spontaneous A-V dissociation.

This analogue represents a simplification and schematization of the events which may be taking place in the A-V node. It is not meant to indicate that the excitation events in the A-V node have these particular forms and time constants, but simply that an analogue of this type will generally explain the clinical features of the A-V arrhythmias more rationally and comprehensively than previous hypotheses. Nor is it meant to indicate that the A-V node morphologically resembles the motor end-plate of skeletal muscle. Rather, it is a confirmation of the doctrine that the principles and properties of excitation are identical in all irritable tissues, whether they be nerve or muscle or specialized organs such as the motor end-plate or the A-V node. To this extent the great progress that has

been made in recent years in neuromuscular physiology may provide technic and information which will lead to greater understanding of cardiac rhythm abnormalities.

SUMMARY

1. Three clinical features of the A-V arrhythmias of acute rheumatic fever are pointed out which are unexplained by previous theories of the mechanism of these arrhythmias and which suggest a different explanation. These are: (*a*) in spite of their frequency the A-V arrhythmias of acute rheumatic fever rarely lead to incomplete or complete heart block, indicating that conduction delay cannot be a prominent part of the mechanism; (*b*) a patient with P-R prolongation due to acute rheumatic fever can be caused at will to develop Wenckebach periods, A-V dissociation or nodal rhythm, suggesting that a single defect is responsible for all these phenomena. When this defect is stable, P-R prolongation is produced; when it is unstable the other arrhythmias are produced; (*c*) there are specific and constant time characteristics of the P-R interval in Wenckebach periods and A-V dissociation which resemble the harmonics of two unstable coupled electronic oscillators.

2. An electronic analogue for the A-V node is described which will reproduce all of these arrhythmias on graded change of only a single parameter. The analogue incorporates properties of electrical events which have been identified in other neuromuscular junctions and in Purkinje tissue. From the performance of the analogue an hypothesis for the mechanisms of the A-V arrhythmias is advanced which explains many clinical aspects of these arrhythmias that have been perplexing in the past. This hypothesis is more consistent with modern excitation theory than are previous explanations.

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The Antemortem Diagnosis of Syphilitic Aneurysm of the Aortic Sinuses*

Report of Nine Cases

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NINETEEN cases of syphilitic aneurysm of the aortic sinuses proved by autopsy have been reported in the English literature since 1914.[1–16] Diagnosis during life was made in only one instance.[14] The aortic sinuses lie deep within the substance of the heart and are inaccessible to physical diagnosis and ordinary radiography. Angiocardiography by visualizing the aortic sinuses readily establishes the diagnosis.

Aneurysms of the aortic sinuses may be congenital or acquired.[16] Congenital aneurysms may sometimes be associated with bicuspid aortic valves,[16–18] coarctation of the aorta,[19] or arachnodactyly;[20] acquired aneurysms may be secondary to bacterial endocarditis,[16,17] dissection of the aorta[16] or syphilis. The purpose of this study is to report the antemortem diagnosis of nine cases of syphilitic aortic sinus aneurysm discovered with the aid of angiocardiography. A review of the nineteen cases recorded in the literature is included in order to emphasize the pathologic, clinical and radiographic features which provide criteria for diagnosis during life.

CASE REPORTS

Diffuse Aneurysmal Dilatation (Aortitis) of Ascending Aorta with Aneurysmal Involvement of Aortic Sinuses

CASE I. A sixty-two year old Negro repairman was admitted to the New York Hospital (No. 587487) on December 14, 1950, complaining of loss of memory. He had dyspnea on exertion and pain in the chest for several weeks, and a non-productive cough of several years' duration. He was unaware of the onset of syphilitic infection and had received no treatment.

Physical examination revealed an elderly man with marked intellectual impairment and recent memory loss. The heart was enlarged and there was pulsation in the third interspace to the right of the sternum. The blood pressure was 154/44; pulse 60, with regular rhythm. A systolic thrill was present in the aortic area; the aortic second sound was absent, a loud to and fro murmur was heard. A diastolic murmur was audible over the entire precordium.

Laboratory study showed the Wassermann test for syphilis to be 4 plus in blood and spinal fluid; the cerebrospinal fluid protein was 105 mg. per cent and there were twenty-three mononuclear cells per cubic millimeter. Electrocardiogram showed normal sinus rhythm with left axis deviation. Conventional frontal chest film (Fig. 1A) showed enlargement of the left ventricle. The ascending aorta was markedly dilated. There was linear calcification in an aneurysmal bulge extending upward from the region of the aortic valves. The descending aorta was also dilated and calcified. Lateral examination of the chest (Fig. 1B) confirmed the presence of a large calcified aneurysm of the proximal aorta arising from the region of the aortic sinuses and eroding the sternum.

Angiocardiographic examination (left anterior oblique projection) on December 26, 1950, revealed opacification of the large fusiform aneurysm of the ascending aorta and demonstrated aneurysmal dilatation of the aortic sinuses. (Figs. 1C and D.) The patient received a series of penicillin injections totalling 6 million units in eighteen days. Examinations over a four-year period disclosed that he had returned to work and was asymptomatic. Roentgenographic findings were unchanged.

CASE II. A fifty-five year old white porter (N.Y.H. No. 454982) was seen in the outpatient department on September 11, 1946, complaining of substernal pain and dyspnea on exertion of one year's duration. Nocturnal dyspnea and ankle edema were absent. There was a history of a chancre thirty-three years previously but serologic examination for syphilis had been negative and the patient had received no treatment.

* From the Departments of Radiology and Medicine of The New York Hospital-Cornell Medical Center, New York, New York. Aided by a grant from the Mallinckrodt Chemical Works.

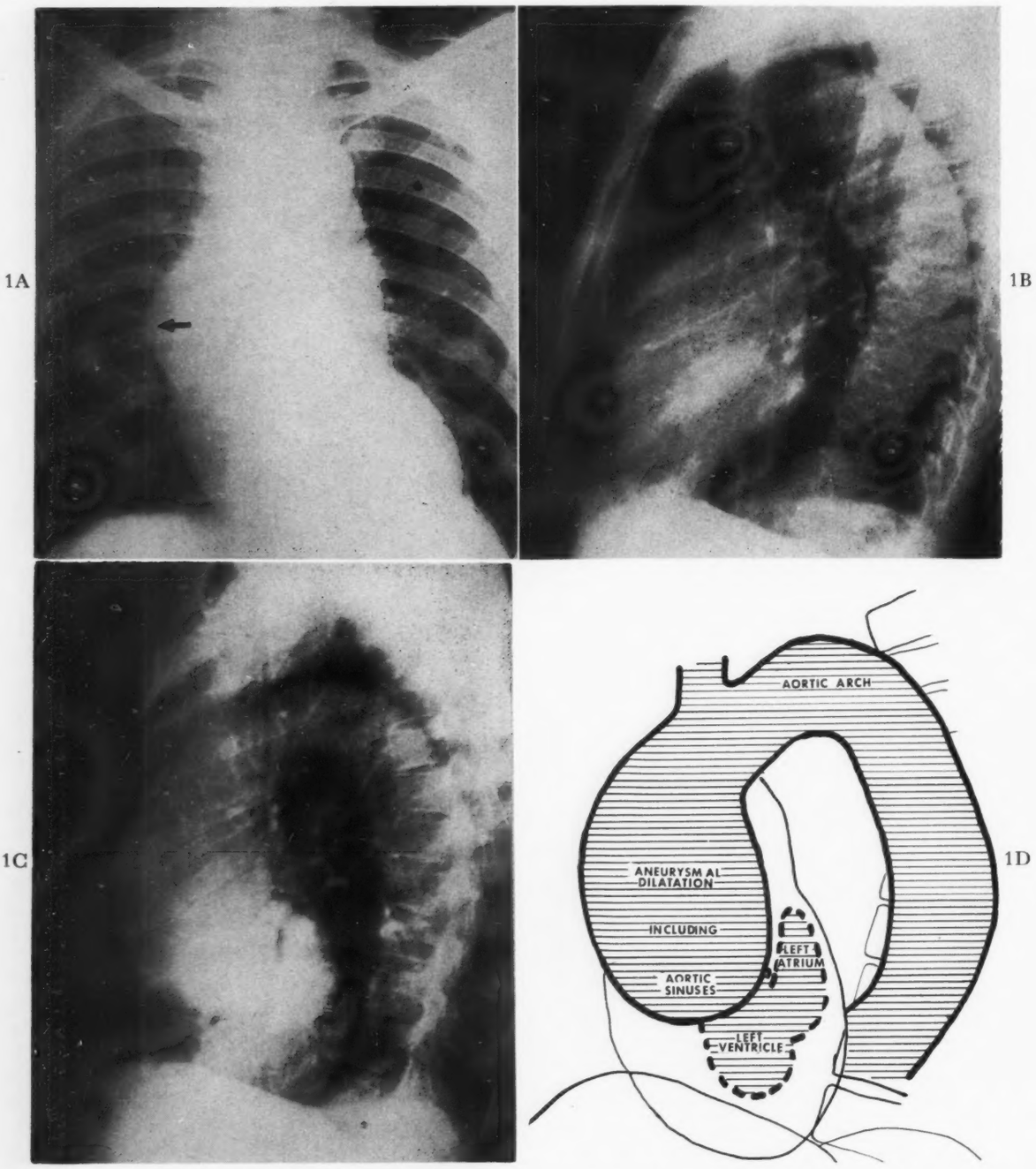


FIG. 1. Case I. A, frontal teleoroentgenogram shows enlargement of the heart, especially of the left ventricle, and a large aneurysm of ascending aorta lined with calcium (arrow). B, left lateral teleoroentgenogram reveals intracardiac calcification outlining a dilated aortic root and the ascending aorta. The descending aorta is dense, sclerotic and widened. C, left anterior oblique angiocardiogram demonstrating aneurysmal dilatation of the aortic sinuses, 6 cm. in diameter, and fusiform dilatation of the proximal aorta. D, tracing of C.

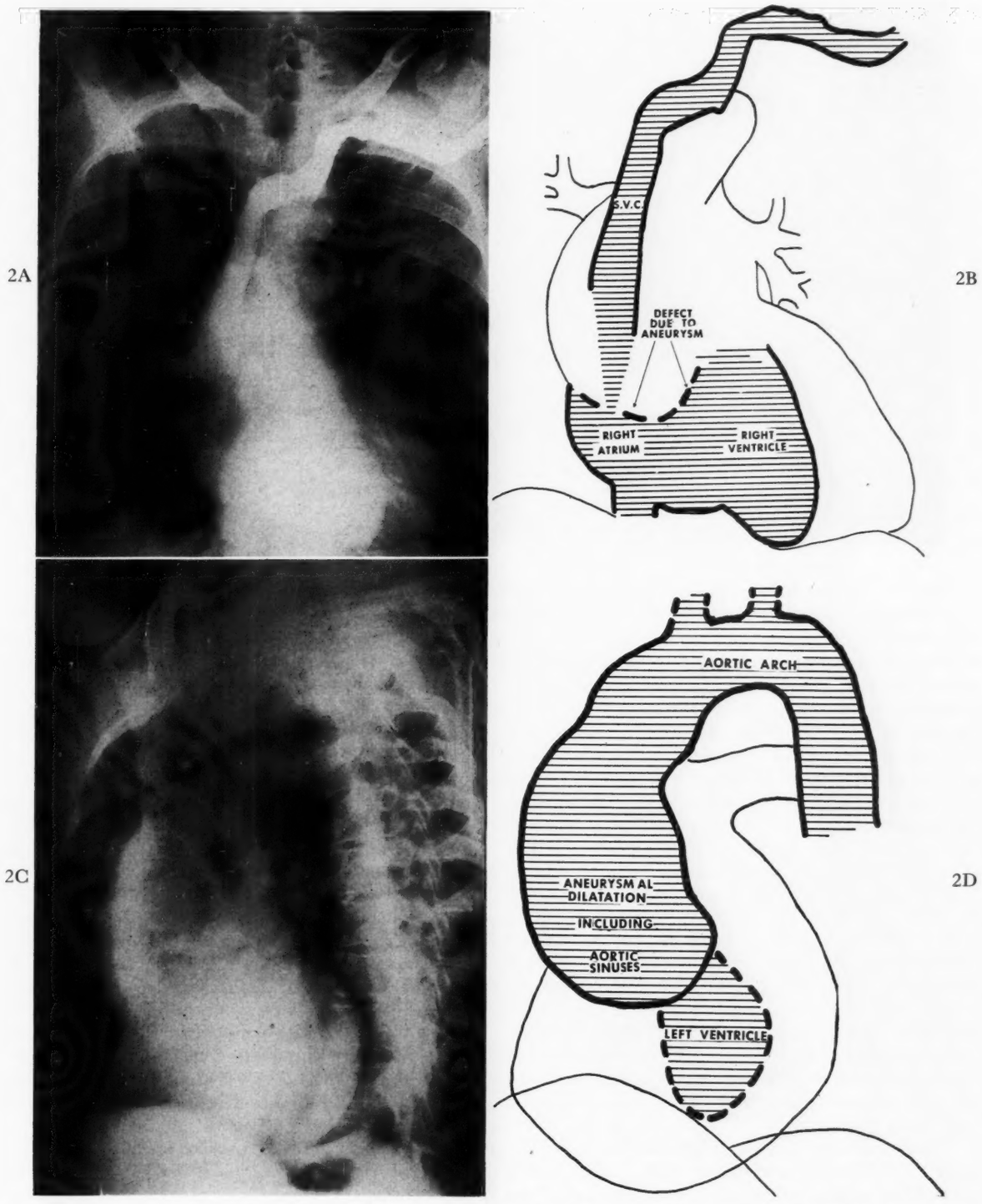
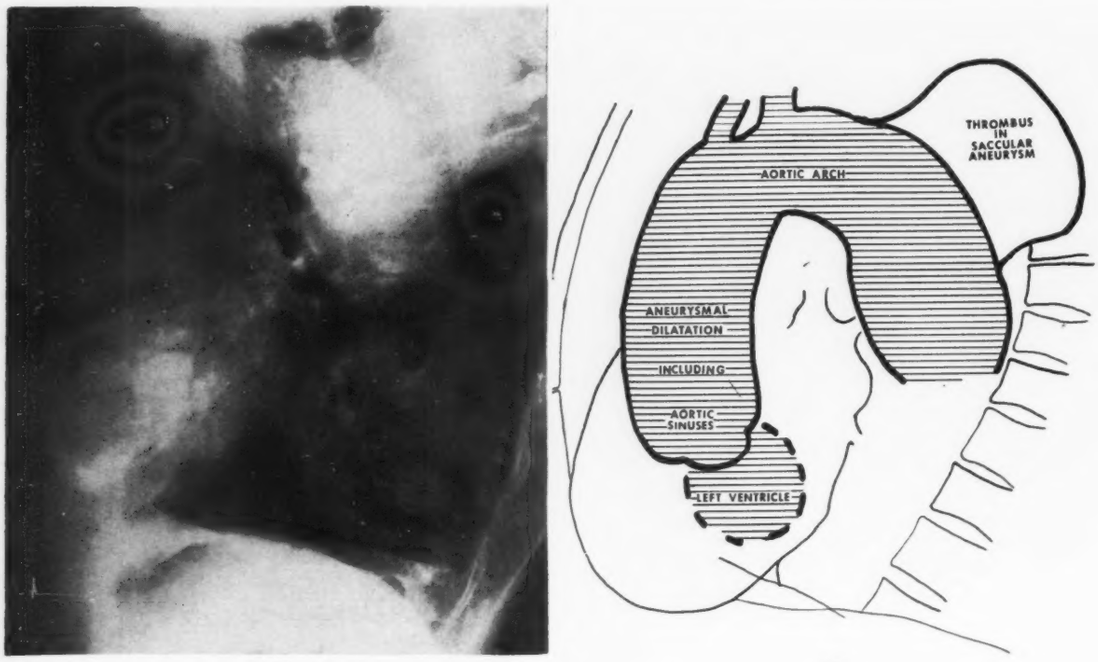


FIG. 2. Case II. A, frontal angiocardiogram showing a filling defect in the right atrium caused by an aortic sinus aneurysm. B, tracing of A. C, left anterior oblique angiocardiogram demonstrates the aneurysmal dilatation of the aortic sinuses (7 cm.) and ascending aorta. D, tracing of C.



3A 3B

FIG. 3. Case III. A, left anterior oblique angiocardiogram reveals aneurysmal dilatation of the aortic sinuses (measuring 6 cm.), ascending and descending aorta, and a saccular aneurysm of the aortic arch. B, tracing of A.

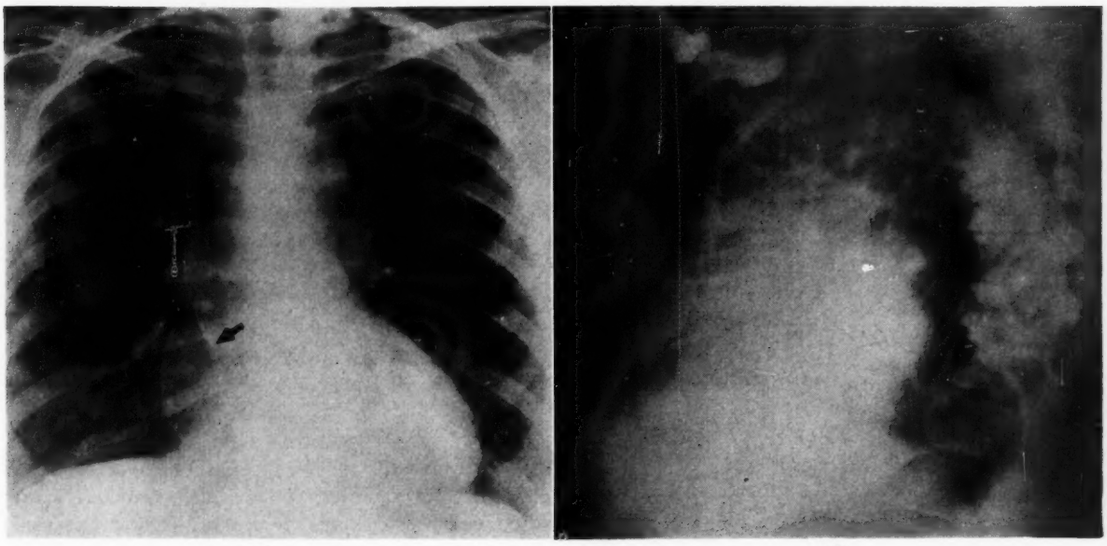
Physical examination revealed an enlarged heart with to and fro systolic and diastolic murmurs over the entire precordium. Peripheral pulses were collapsing in character and the blood pressure was 230/60. There was no peripheral edema; however, the neck veins were distended. The Wassermann test gave a negative reaction and the Mazzini test gave a doubtful result. The electrocardiogram showed normal sinus rhythm, left axis deviation, and split P waves. The chest roentgenogram showed an enlarged heart with marked prominence of the left ventricle and aneurysmal dilatation of the ascending aorta. Calcification was present in the wall of the aneurysm. Angiocardiographic examination on September 17, 1946, in frontal and left anterior oblique views (Figs. 2A to D) showed a huge aneurysmal dilatation of the aortic sinuses and ascending aorta, with narrowing of the superior vena cava as it entered the heart and a filling defect of the right atrium due to the aneurysm. The patient did not return for treatment.

CASE III. A fifty year old white male clerk (N.Y.H. No. 570784) was admitted on July 3, 1950 with a complaint of pain of one year's duration over the left scapula. A few months prior to admission he had had pain in the left anterior chest and a persistent non-productive cough. At sixteen years of age he had had a penile lesion and an urethral discharge treated only by local irrigations.

On physical examination a few inspiratory rales were present at the bases of the lungs. Auscultation of the heart revealed a soft systolic murmur at the apex and a soft blowing diastolic murmur in the second right interspace; the blood pressure was 125/70. There was no peripheral edema. Laboratory examination revealed the blood and cerebrospinal fluid Wassermann tests to be 4 plus; the cerebrospinal protein was 55 mg. per cent. The electrocardiogram showed normal sinus rhythm and left axis deviation. Roentgenogram of the chest revealed right dorsal scoliosis and enlargement of the left ventricle. There was fusiform enlargement and calcification of the ascending aorta and a large saccular aneurysm in the distal transverse aorta. Angiocardiographic examination on July 16, 1950, in the left anterior oblique projection revealed aneurysmal dilatation of the ascending aorta including the sinuses of Valsalva, and a huge laminated clot in the saccular aneurysm of the transverse aorta. (Figs. 3A and B.)

Treatment consisted of a total dose of 7.2 million units of penicillin. After discharge from the hospital the patient moved to Florida. He died suddenly on November 28, 1951, with severe precordial pain and probable rupture of an aneurysm. No autopsy was performed.

CASE IV. A forty-five year old Negro housewife (N.Y.H. No. 87290) was admitted on October 2, 1950, for excision of a large myomatous uterus. Examination revealed hypertension and enlargement of the heart. The patient was asymptomatic except for occasional episodes of palpitation. In 1934 she had been told by a physician that she had heart



4A 4B

FIG. 4A and B. Case IV. A, frontal teleoroentgenogram shows an enlarged heart, especially the left ventricle. The ascending aorta is dilated and contains calcium (arrow) in the intracardiac origin of the aorta. B, left anterior oblique angiocardiogram shows the aneurysmal dilatation of the aortic sinuses (5.5 cm.) and ascending aorta.

disease; a year later the Kline test was positive but no treatment for syphilis was given.

Physical examination disclosed an obese woman in no distress. The heart was enlarged and systolic and faint diastolic thrills were felt in the aortic area. A harsh (grade 3) systolic murmur radiating toward the neck and a loud (grade 2) diastolic murmur were heard in the aortic area radiating along the left sternal border. The blood pressure was 250/100. Electrocardiographic studies (multiple chest leads) disclosed normal sinus rhythm, left axis deviation and left ventricular hypertrophy. Hysterectomy was not advised because of the cardiovascular disease.

Routine roentgenograms of the chest showed left ventricular enlargement. The aorta was dilated and elongated, with calcification along the proximal ascending aorta in the region of the aortic sinuses. (Fig. 4A.) Angiocardiography on October 5, 1950, demonstrated aneurysmal dilatation of the ascending aorta including the aortic sinuses, with hypertrophy of the left ventricular wall. (Figs. 4B and C.) After a full course of penicillin therapy (total dosage, 6.6 million units) she continued to be asymptomatic. When last seen in 1954, the aortic murmurs and hypertension were unchanged.

CASE V. A fifty-three year old white laborer (N.Y.H. No. 206926) was seen in 1938 because of right pleuritic pain and exertional dyspnea. He had had gonorrhea at fifteen years of age and syphilis at eighteen. Examination showed blood pressure of 125/80; the heart was normal except for a loud ringing second aortic sound. The patient was found to have active pulmonary tuberculosis. Kline and Wassermann tests were positive but the patient refused treatment and attended the clinic at rare intervals. In 1947 he returned because of a marked increase in dyspnea on exertion. Examination disclosed a blood pressure of 185/80 and an enlarged heart. There was a loud, harsh systolic murmur in the aortic area. The aortic second sound was replaced by a loud, blowing diastolic murmur. There were no signs of heart failure.

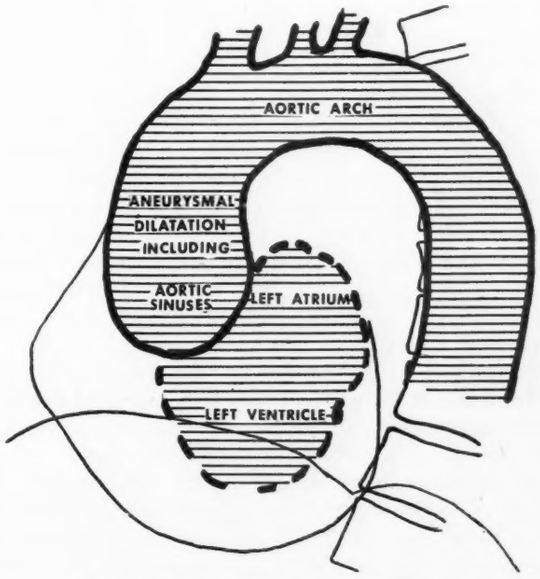


FIG. 4C. Case IV. Tracing of Figure 4B.

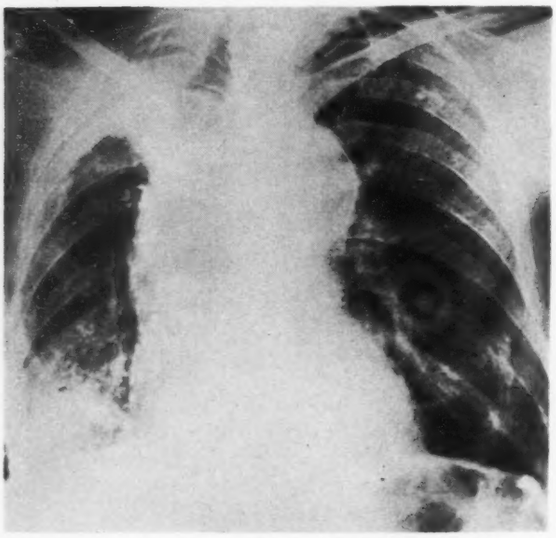


FIG. 5. Case v. Frontal teleoroentgenogram shows deviation of the trachea toward a dense right apex, and fibrosis of the right lung. The pleura at the right base is calcified and there are scattered pulmonary calcifications throughout the left lung. The heart is enlarged and the aorta is widened and tortuous with calcification along the entire ascending and descending portions.

Roentgenogram of the chest (Fig. 5) showed bilateral calcific pulmonary and pleural tuberculosis, most marked on the right with consolidation and fibrosis at the right apex. The heart was enlarged. The aorta was dilated, elongated and unfolded, with calcification in the ascending, arch and descending portions. Angiocardiography on December 23, 1947, showed aneurysmal dilatation of the aorta including the aortic sinuses, and hypertrophy of the left ventricle. The electrocardiogram showed left axis deviation. The patient again refused treatment and was last seen on August 13, 1952, with congestive heart failure and auricular fibrillation.

CASE VI. A fifty-one year old laborer (N.Y.H. No. 616021) complained of dyspnea on exertion which began abruptly after an attack of anterior chest pain five years before hospital admission. He denied any previous illness or syphilitic infection. On examination the heart was enlarged and there were soft systolic and diastolic murmurs at the aortic area. The blood pressure was 144/80. The Mazzini test was negative. Roentgenogram of the chest revealed enlargement of the left ventricle and calcification of a mass adjacent to the ascending aorta. In the lateral view (Fig. 6A) a large rounded calcific shadow appeared in the intracardiac portion of the ascending aorta. Angiocardiographic studies were performed on November 27, 1951, and showed a huge retrosternal sacculated aneurysm of the ascending aorta associated with aneurysmal dilatation of the aortic sinuses, and an enlarged left ventricle. (Fig. 6B.) Electrocardiogram revealed left axis deviation and left ventricular hypertrophy. The patient received a total of eight million units penicillin; when last seen early in 1955, he felt improved and was doing light work.

Syphilitic Aortitis with Localized Aneurysm of Aortic Sinuses

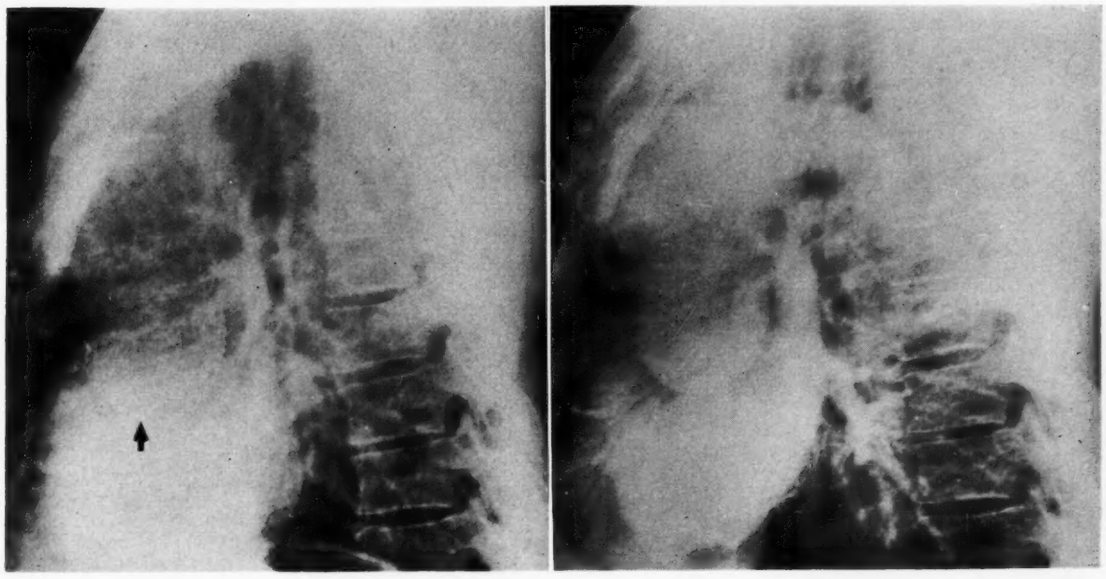
CASE VII. A fifty-seven year old Negro porter (N.Y.H. No. 166584) was seen on September 6, 1946, because of dyspnea and ankle edema of eight years' duration. Seven years previously, after a pre-employment examination, he was told that his blood pressure was high and that he had an enlarged heart. The serologic test for syphilis was positive and he received a course of sixteen injections. Because he felt well, he stopped treatment.

Examination revealed pronounced sacral and leg edema, moist rales at the bases and an enlarged tender liver. A long harsh systolic murmur over the aortic area was transmitted toward the neck; a harsh decrescendo diastolic murmur radiated downward along the left sternal border. The blood pressure was 240/90. Electrocardiographic studies (multiple chest leads) disclosed normal sinus rhythm, left axis deviation, left ventricular hypertrophy, and peaked P waves suggestive of left auricular hypertrophy. Roentgenograms of the chest showed an enlarged heart with predominant enlargement of the left ventricle. The aorta was elongated and showed calcification in the ascending portion. Angiocardiography on October 16, 1947, (Fig. 7) showed a large localized aneurysmal dilatation of the aortic sinuses and a fusiform dilatation of the descending aorta. The ascending aorta above the aortic sinus aneurysm was of normal dimensions.

The patient improved after mercurial diuretics and digitalis and was discharged without evidence of cardiac failure. He remained well for four months but died suddenly on February 3, 1948 while at work; no autopsy was performed.

CASE VIII. A forty-nine year old Negro laborer was admitted to Christ Hospital, Cincinnati, Ohio, on January 18, 1950, following the discovery of a mediastinal mass on routine chest roentgenography. The patient had no complaints but for six months had noted some dyspnea on exertion. He had had a penile lesion as a young man and ten years before had received a course of treatment for syphilis.

On examination a loud systolic murmur was heard along the left sternal border from the second to fourth interspace; the blood pressure was 135/80. Fluoroscopic examination revealed vigorous pulsations of the mass synchronous with the heart beat. A roentgenogram of the chest (Fig. 8A) showed a large calcified round mass arising within the heart in the region of the aortic sinuses and extending anteriorly to the sternum. The heart was enlarged; the left upper cardiac border was prominent and the left ventricle enlarged. The aorta was slightly



6A 6B

FIG. 6. Case VI. A, lateral teleoroentgenogram shows a dilated calcified ring-like structure outlining the aortic sinuses. Above, in the ascending aorta, there is a large retrosternal aneurysm lined by calcium. B, left lateral angiocardiogram reveals the huge aneurysmal dilatation of the aortic sinuses (5.5 cm.) and ascending aorta.

elongated, with some calcification of the arch. Results of angiocardiography performed on January 21, 1950 (Figs. 8B and C), by Dr. Edward C. Elsey, showed a large localized aneurysm of the aortic sinuses with laminated calcified clot at the anterior margin of the aneurysm. Recent communication with Dr. Elsey disclosed that the patient failed to return for examination.

CASE IX. A sixty-four year old white laborer (N.Y.H. No. 651088) was referred for angiocardiography by Dr. Samuel Millman who had observed calcification in the region of the left atrium. The patient complained of dyspnea on exertion and anterior chest pain. He had had gonorrhea in 1930; and in 1932 a routine blood Wassermann test gave positive results. The patient was then treated with bismuth and salvarsan.® At that time he was given digitalis for a "leaky heart valve." In 1952 exertional and nocturnal dyspnea and attacks of anterior chest pain again became severe.

Physical examination showed the heart to be enlarged. A soft blowing systolic murmur was audible over the entire precordium and a decrescendo diastolic murmur was heard at Erb's point immediately following the second sound. The second sound in the pulmonic area was louder than in the aortic area. Basal rales were present, the liver was enlarged, and there was minimal ankle edema. The blood pressure was 140/80. The Kolmer serum cardiolipin test was positive (4 units). Electrocardiographic examination showed first degree heart block, low voltage and clockwise rotation of the heart. Roentgenograms of the chest (Figs. 9A and B) showed an enormous cardiac silhouette, enlarged in all diameters with prominence of the pulmonary artery segment. A large rounded calcified mass occu-

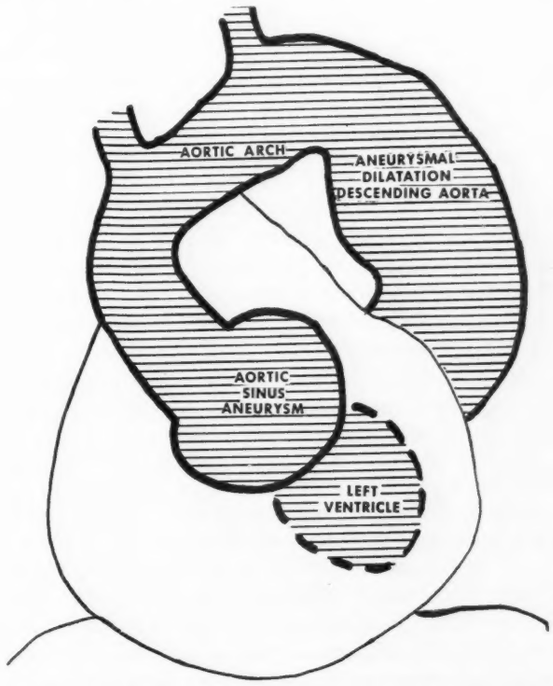
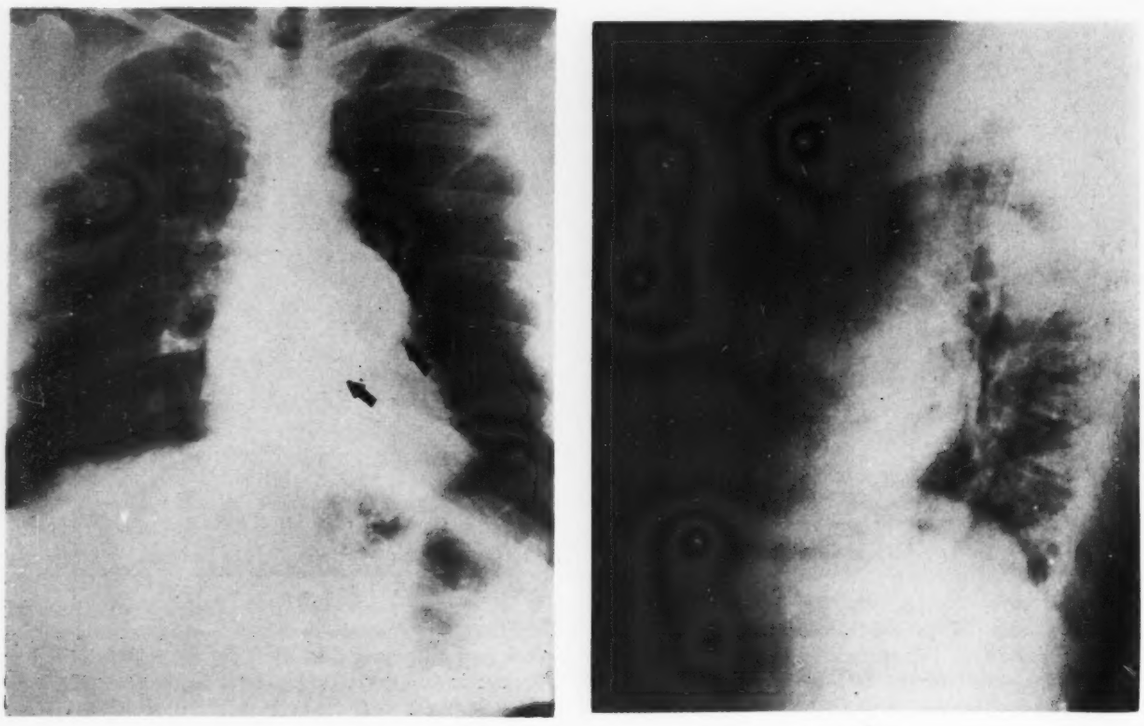


FIG. 7. Case VII. Tracing of left anterior oblique angiocardiogram demonstrating a localized aneurysm of the aortic sinuses (measuring 7.2 cm.). (From DOTTER, C, T. and STEINBERG, I. Angiocardiography. New York. 1951. Paul B. Hoeber, Inc.)



8A 8B

FIG. 8A and B. Case VIII. A, frontal teleoroentgenogram shows a calcified mass in the region of the pulmonary artery (arrows). B, left lateral angiocardiogram reveals a saccular aneurysm of the aortic sinuses surrounded by calcified laminated thrombus measuring 9.5 cm. in diameter.

pied the entire right portion of the heart and extended from the sternum to the esophagus. (Fig. 9B.) The barium-filled esophagus was displaced posteriorly as if by an enlarged left atrium. There was extensive calcification of the ascending aorta and arch. Angiocardiography performed on March 10, 1953, in the left anterior oblique projection (Figs. 9C and D) showed the calcified mass to be a large, localized aneurysm of the aortic sinuses with laminated clot. There was only slight dilatation of the ascending aorta. In the frontal projection (Figs. 9E and F) there was evidence of pressure on the superior vena cava, right atrium, right ventricle and pulmonary artery. There was also marked narrowing of the right branch of the pulmonary artery.

Since angiocardiographic examination there has been little change in the symptoms, cardiac size or roentgenographic appearance of the calcified aortic sinus aneurysm. An electrocardiogram on December 11, 1954, disclosed normal sinus rhythm with first degree heart block (P-R interval, 0.26 sec.), low voltage in the limb leads, slight right axis deviation, a semivertical position with clockwise rotation of the heart, and prominent precordial S waves.

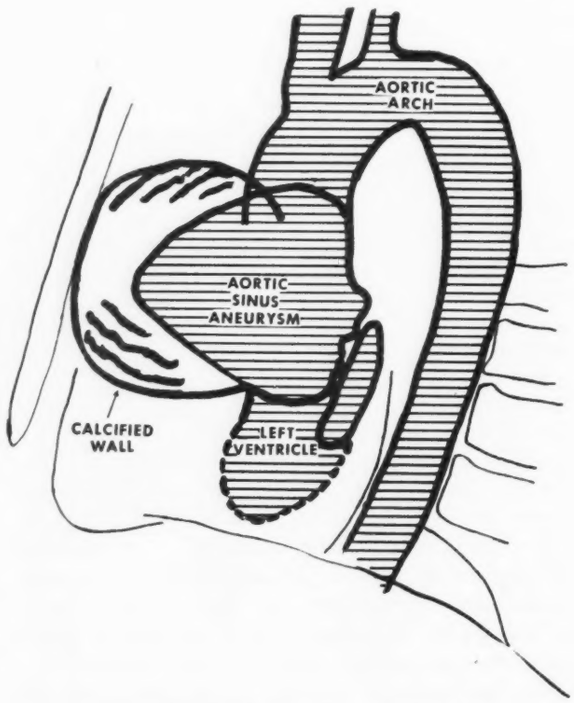
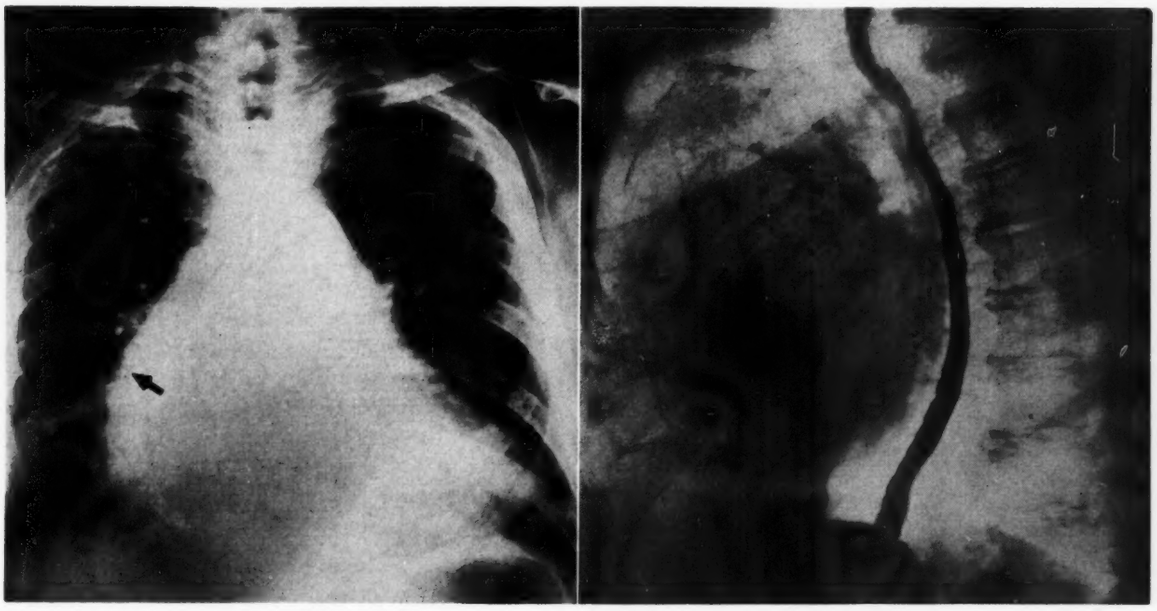


FIG. 8C. Case VIII. Tracing of Figure 8B.

COMMENTS

Normal Anatomy of Aortic Sinuses; Terminology. The aortic sinuses are three small dilatations in



9A 9B

FIG. 9A and B. Case IX. A, frontal teleoroentgenogram reveals marked cardiac enlargement. A huge calcified mass is present along the upper right cardiac border and there is prominence of the pulmonary artery segment. B, left lateral esophagram (contact film) shows to advantage the massive calcification of the ascending aorta and the mass displacing the esophagus posteriorly.

the wall of the aorta immediately above the aortic valves. Each sinus lies just above the attachment of an aortic cusp. The right and left coronary arteries usually originate within two of the aortic sinuses; however, they may emerge immediately distal to the aortic sinuses. The aortic sinuses and their corresponding aortic valves are named according to the source of the coronary arteries. Thus the right and left coronary arteries emerge from the right and left aortic sinus, respectively. The remaining aortic sinus usually lies posteriorly and does not contain a coronary artery. According to the newest nomenclature it is designated the non-coronary sinus.[16]

The aortic sinuses are intracardiac and cannot be identified on conventional roentgenography. During angiocardiography they appear as dilatations at the root of the aorta immediately above the aortic valves and are best visualized in the left anterior oblique projection.[22] Inconstant filling of the coronary arteries during angiocardiography does not always allow identification of the individual sinuses. However, in the left anterior oblique view the right coronary sinus is anterior and just behind the sternum. The aortic sinuses are in close relation to all the cardiac chambers, particularly the right atrium and ventricle.[12,16] The origin of the pulmonary artery, the interventricular septum and the left atrium are adjacent while the superior vena cava is more distant.

Pathology and Classification. Syphilis of the cardiovascular system is most common at the aortic valve and ascending aorta. The intimal surface of the aorta and the elastic fibers of the media are gradually weakened and destroyed. The pulsating aorta then expands, with diffuse dilatation or formation of a localized saccular aneurysm. Calcium is frequently deposited in plaques in the damaged intima. If the aneurysm is large, vascular stasis occurs and a laminated thrombus may partially fill the lumen. Dilatation of the valve ring frequently produces valvular insufficiency. Similarly, there may be involvement of the aortic sinuses with aneurysmal dilatation or saccular aneurysm.

Nineteen cases of syphilitic aneurysms of the aortic sinuses, proved by autopsy, have been reported in the English literature since 1914. (Table I.) All these aneurysms were saccular and were associated with syphilitic aortitis. Three of our patients (Cases VII, VIII and IX) were of this type. In contrast, there are six patients (Cases I to VI) with aneurysmal dilata-

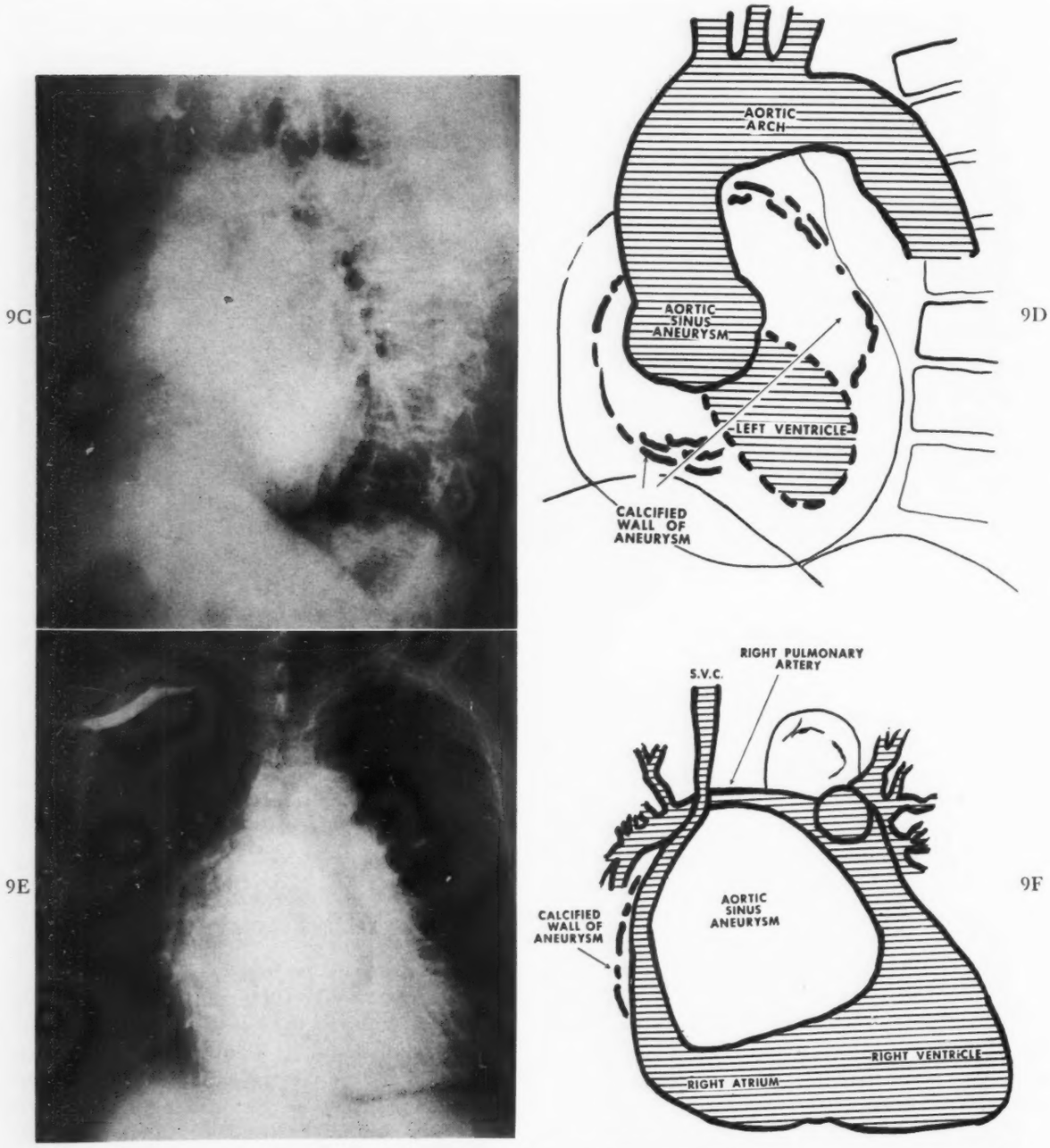


FIG. 9C to F. Case IX. C, left anterior oblique angiocardiogram reveals an aortic sinus aneurysm surrounded by calcified thrombus measuring 13 cm. in diameter. D, tracing of C. E, frontal angiocardiogram demonstrates marked right ventricular enlargement with narrowing of the main pulmonary artery and its right branch. F, composite tracing of E and earlier angiocardiographic films (not illustrated).

tion of the aortic sinuses in continuity with a fusiform aneurysm of the ascending aorta. In the literature, the latter group is not separated and is probably included among patients who have syphilitic aortitis with insufficiency. However, recognition of the aortic sinus aneurysm as a separate entity is made possible by angiocardiography. These diffuse aneurysms of the aortic sinuses are clearly recognized because of the localized enlargement and pressure effects upon adjacent cardiac structures.

A series of fifty-nine normal patients of the same age group as our cases on angiocardiography showed an average width of the aortic

sinuses of 37 mm., with a variation from 30 to 49 mm. All our patients with syphilitic aneurysmal dilatation of the aortic sinuses showed measurements well above 50 mm. The average was 62 mm. and the range, from (55 to 130 mm.).

Unlike congenital and mycotic aneurysms of the aortic sinuses, syphilitic aneurysms may become very large before they rupture.[3,11,16] In seven of the nineteen cases in the literature such aneurysms were more than 4 cm. in diameter. In the literature (Table I) each of the aortic sinuses has been reported as the site of origin of a syphilitic aneurysm. In two instances the aneurysmal sac occupied two sinuses. This is in contrast to the sites of origin of congenital aortic sinus aneurysms. Morgan-Jones and Langley[16] state that the proved congenital aortic sinus aneurysms involve only the right and non-coronary sinuses.

Visualization of the coronary arteries with angiocardiographic technic is uncertain, hence individual identification of the aortic sinuses is not always possible. All of the aortic sinuses appear to be involved in Cases I to VI. However, outpouchings from a single sinus obscuring the other two cannot be disproved. In contrast, Cases VII, VIII and IX are examples of localized aneurysms of the aortic sinuses.

In eleven of the nineteen cases recorded in the literature (Table I) there was rupture of the aortic sinus aneurysm whereas in all of our cases perforation did not occur. Contrary to reports,[12] there is no predictable relationship between the sinus of origin and the structure into which perforation occurs. In eight of the eleven cases reported (73 per cent) the aneurysm ruptured into the lesser circulation: pulmonary artery, four; right atrium, two; and right ventricle, two. These produced a left-to-right shunt. Syphilitic aortic sinus aneurysms, unlike the congenital aneurysms, may rupture outside the heart.[3,8,16,17] This is probably because the syphilitic aneurysms may attain such a large size prior to perforation.

The most common cause of death in patients with syphilitic aortic sinus aneurysm, even with rupture, was cardiac failure. In eight cases perforation with the establishment of an internal aorticocardiac fistula or aorticopulmonary fistula hastened failure; none of these patients survived more than two months following this event. Rupture outside the heart was followed by sudden death within minutes to hours. A coronary artery was found to be occluded due to the presence of an adjacent aortic sinus aneurysm in four instances. (Table I.) In two cases myocardial infarction was found distal to the occluded left coronary artery and was the immediate cause of death.[13] In another case the aneurysm was intact but bulged into the interventricular septum and pulmonary conus, producing stenosis immediately below the pulmonary valve; as a result there was delayed A-V conduction apparently due to pressure on the adjacent bundle of His.[8]

The incidence of calcification among the nineteen reported cases cannot be established accurately because of inadequate description in the protocols. Grossly visible calcification of the aneurysmal wall was recorded in four instances and in the ascending aorta three times. Radiographic demonstration of calcification in the aneurysm, however, has been reported only once.[15] This is in contrast to the roentgenographic finding of linear calcification in the ascending aorta or aneurysm in all our patients.

CLINICAL ASPECTS

Age, Sex and Race. Our patients ranged in age from forty-five to sixty years, with an average of fifty-four years. In contrast is the age range of the cases reported in the literature (seventeen to sixty years). Of sixteen cases in which the age was recorded, six of the patients (37 per cent) were under thirty years. The reason for the age difference is not readily apparent; no statement regarding the stigmas of congenital syphilis was recorded.

Males predominated in the reported cases (Table I) and in our series only one patient (Case IV) was a woman. The majority of the patients in the reported cases (Table I) were Negro; in our series there were five Caucasian and four Negro patients.

Symptoms and Signs. As a rule, aortic sinus aneurysms do not produce symptoms or signs prior to rupture. Rather, the dilatation of the aortic sinuses or syphilitic involvement of the aortic valvular ring produces aortic insufficiency and heart failure. All but one of our patients had aortic incompetence, evidenced by aortic diastolic murmurs, bounding pulses or wide pulse pressures. In two patients (Cases VI and IX) heart failure was present during their illnesses. Precordial pain, probably due to coronary osteal stenosis, occurred in several patients (Cases II, III, V, IX).

Blood Pressure. A prominent feature in the

TABLE 1

REVIEW OF LITERATURE ON SYPHILITIC AORTIC SINUS ANEURYSMS (DIAGNOSED AT AUTOPSY)

Case and Reference	Age, Sex and Race	Symptoms and Signs	Blood Pressure	Sinus Involved	Perforation into	Roentgen Findings	Autopsy Findings	Remarks
1, Smith[1]	17,F,N	6 wk. dyspnea, edema of legs, thrill and rasping to and fro murmurs 3rd left I.S.*	.....	Right	.....	Generalized cardiac enlargement, especially right ventricle	Small aortic sinus aneurysm	.....
2, Smith[1]	26,F,N	2 mo. dyspnea and peripheral edema; physical findings similar to Case 1	.....	Right	Pulmonary artery	Cardiac enlargement, especially right side	Small aortic sinus aneurysm with perforation near pulmonary valve	.....
3, Scott[2]	51,F,N	2 mo. dyspnea and peripheral edema; thrill and harsh systolic and diastolic murmurs, left 2nd and 3rd I. S.	116/30	Right	Pulmonary artery	Generalized cardiac enlargement, base wide	Right aortic sinus aneurysm with 2 pockets (4–5 cm. diameter), one perforating near pulmonary valve	Right coronary artery occluded
4, Scott[2]	29,M,N	3 wk. dyspnea, peripheral edema, ascites; thrill, loud machinery murmur in left 2nd I. S.	140/40	Left	Pulmonary artery	Slight generalized cardiac enlargement	Left aortic sinus aneurysm 4.5 cm. diameter bulging into pulmonary conus and perforating near pulmonary valve	.....
5, Sheldon[3]	49,M,?	11 mo. pulsating mass anterior chest wall; no dyspnea; systolic and diastolic murmurs	210/80	Right	External structures	.....	Large right aortic sinus aneurysm with perforation through sternum	.....
6, Snyder, Hunter[8]	?	Autopsy specimen only	.....	Left	.....	.....	Left aortic sinus aneurysm (3 cm. diameter) narrowing pulmonary conus with dilatation of right ventricle	Also aneurysm at left coronary artery with recent thrombus and infarct, probable immediate cause of death
7, Snyder, Hunter[8]	60,M,W	3½ mo. dyspnea and ankle edema; loud to and fro murmur in aortic and mitral area	160/35	Non-coronary	.....	.....	Non-coronary aortic sinus aneurysm (2.8 cm. diameter) in I. V.† septum near A-V bundle, narrowing pulmonary conus	Electrocardiogram 1° heart block
8, Schuster[11]	53,M,?	6 yr. pulsating left chest wall, dyspnea and angina; thrill and systolic and diastolic murmurs	.....	Right	Left pleural space	Pulsating mass below left pulmonary artery; generalized cardiac enlargement	Large (size of "2 fists") right aortic sinus aneurysm with perforation	Right coronary artery occluded by aneurysm
9, Norris[8]	20,F,N	6 wk. dyspnea and peripheral edema; thrill, loud systolic and diastolic murmurs over precordium	110/68	Left and non-coronary	.....	Cardiac enlargement	Aortic sinus aneurysm (3.5 cm. diameter) arising from adjacent areas of non-coronary and left aortic sinus	.....
10, Higgins[9]	52,M,N	1 wk. paresis of right arm and face; thrill, to and fro murmur, mitral area; death 1 hr. after sudden dyspnea	.....	Left	Right atrium	.....	Left aortic sinus aneurysm (1 cm. diameter) with perforation	.....

TABLE I (*Continued*)

Case and Reference	Age, Sex and Race	Symptoms and Signs	Blood Pressure	Sinus Involved	Perforation into	Roentgen Findings	Autopsy Findings	Remarks
11, Wright[10]	27,M,N	46 days sudden dyspnea chest pain; thrill, pulmonary area; systolic and diastolic murmurs, mitral area	140/20	Right	Right atrium	.....	Right aortic sinus aneurysm (1 cm. diameter) with perforation near tricuspid valve	.....
12, Ostrum et al.[12] (Case v)	38,M,N	2 mo. dyspnea, chest pain; continuous murmur in left 2nd I. S.	150/50	Left	.....	Large heart, "mitral type" without evidence of left atrial enlargement	Left aortic sinus aneurysm (3 cm. diameter) compressing pulmonary artery; right heart dilated	.....
13, Chipps[13]	39,M,W	1 yr. exertional dyspnea; 4 days severe chest pain	100/84	Left	.....	Pulmonary congestion	Left aortic sinus aneurysm (2.3 cm. diameter) compressing left coronary artery; myocardial infarct distally	Death due to myocardial infarction
14, Tompkins[14]	47,M,W	17 days dyspnea; systolic and diastolic thrill and loud murmurs in left 3rd I. S.	146/30	Left	Right ventricle	Large heart with prominent pulmonary artery	Left aortic sinus aneurysm (2.5 cm. diameter) with perforation near pulmonary valve	Diagnosed clinically during life; electrocardiogram; no axis deviation
15, Benson et al.[7]	?,M,?	Progressive dyspnea	.....	Left	.....	.....	Saccular aneurysm of ascending aorta, one pouch involving left aortic sinus	.....
16, Schwab, Sanders[4]	28,M,N	1½ mo. sudden dyspnea, chest pain; thrill, loud systolic and diastolic murmurs to left of sternum	120/10	Non-coronary	Right ventricle	Large heart, dilated aorta	Small non-coronary aortic sinus aneurysm perforating near pulmonary valve; large aneurysm of ascending aorta also present	Electrocardiogram; right axis deviation
17, Abbott[5]	?	Museum specimen	.....	Right and non-coronary	Anterior mediastinum	.....	Aortic sinus aneurysm "size of a man's fist" arising from fused right and non-coronary sinuses with perforation; bulge also into right atrium and pulmonary conus	Ascending aorta diffusely dilated and calcified
18, Abbott[5]	31,M,N	Dyspnea	.....	Left	.....	.....	Left aortic sinus aneurysm, "size of a butternut" with secondary sacculations	.....
19, Shipp et al.[15]	52,M,?	5 wk. sudden dyspnea; continuous thrill and systolic and diastolic machinery murmurs loudest in left 2nd and 3rd I. S.	150/50	Left	Pulmonary artery	Large heart, prominent pulmonary artery segment, calcification simulating left atrial enlargement	Left aortic sinus aneurysm (9 cm. diameter) with perforation	Electrocardiogram; right axis deviation

* I. S. = interspace.
† I. V. = interventricular.

reported cases (Table I) and of our cases of syphilitic aortic sinus aneurysm was a low diastolic pressure, systolic hypertension and high pulse pressure. This is related to the aortic insufficiency. Four of our patients (Cases III, VI, VIII and IX), however, had normal blood pressure.

Electrocardiography. Electrocardiographic examination in seven of our cases showed either left axis deviation or left ventricular hypertrophy. These findings reflect the enlargement of the left ventricle due to aortic regurgitation and hypertension. In one patient (Fig. 9) there was right axis deviation and first degree heart block. In this instance (Figs. 9E, F) compression of the pulmonary conus, pulmonary artery and right branch by the aneurysm was demonstrated and this is believed to have caused chronic cor pulmonale.[23] In the literature, two cases exhibiting right axis deviation of the electrocardiogram were associated with perforation of the aortic sinus aneurysm into the lesser circulation.[4,15] This is probably due to acute cor pulmonale resulting from overloading, and hypertension of the right heart.

DIAGNOSIS

During life the diagnosis of aortic sinus aneurysm should be suspected whenever there is syphilitic aortic regurgitation and linear calcification of the ascending aorta. The diagnosis can be made with certainty if the calcification extends downward and into the intracardiac origin of the aorta and the contour suggests dilatation of the aortic sinuses (Figs. 1B and 6B); or if there is massive calcification in this region (Figs. 8B and 9B). Angiocardiography affords confirmation of the diagnosis. The angiocardiographic demonstration of aortic sinus aneurysm has been reported three times[21,22,24,25] and retrograde aortography has revealed congenital aneurysm of the right aortic sinus.[26]

Rarely, a patient with right heart enlargement, right axis deviation of the electrocardiogram, and calcification near the left atrium may be mistaken for rheumatic heart disease with mitral and aortic valvular involvement and calcification of the left atrium. (Fig. 9.)[15] However, the presence of linear calcification in the ascending aorta should suggest the syphilitic etiology.[27,28]

Sudden onset of severe dyspnea, overloading of the right side of the heart and failure, enlargement of the pulmonary artery, and evolution of machinery-like murmurs should call attention to the possibility of rupture of an aortic root aneurysm into the pulmonary artery or right heart chambers.[29] A recent attempt to repair a ruptured aortic sinus aneurysm was not successful.[30]

TREATMENT AND PROGNOSIS

Early diagnosis and adequate treatment of syphilis with penicillin will prevent aortitis and aneurysms.[31] The discovery of an aortic sinus aneurysm is not always ominous. Of our nine patients, two are dead (Cases III and VI); three were lost to observation (Cases II, VI and VII); and four are alive and have been under medical care for periods up to five years. In all those living, penicillin therapy was given and this may have been a factor in prolonging life.

Surgical repair of a syphilitic sinus of Valsalva aneurysm is a formidable undertaking. The attempt to repair a ruptured congenital aortic sinus through the right atrial approach is feasible.[30] The congenital types are usually small, localized and do not tend to compromise the neighboring cardiovascular structures to as great a degree.

SUMMARY AND CONCLUSIONS

Nine patients with syphilitic aortic sinus aneurysms diagnosed during life by angiocardiography are reported and the findings compared with those in nineteen cases diagnosed at autopsy which were reported in the literature. The diagnosis was made prior to rupture in our patients.

Two groups can be recognized: aortic sinus aneurysms associated with fusiform dilatation (aortitis) of the ascending aorta (six cases); and localized aortic sinus aneurysms (three cases). Unlike congenital aneurysms of the sinus of Valsalva, syphilitic aneurysms may be huge and occasionally rupture outside the heart.

Clinically, aortic regurgitation is an outstanding feature of aortic sinus aneurysms and was present in all but one of our cases. Next in importance is heart failure, often intractable. Rupture of an aneurysm with creation of an aorticocardiac shunt is characterized by the presence of harsh machinery-like murmurs associated with overloading of the right heart chambers and the pulmonary arterial system. Rupture of an aortic sinus aneurysm into the lesser circulation is not always immediately

fatal; rupture outside the heart always causes sudden death.

The usual electrocardiographic findings of unperforated syphilitic aortic sinus aneurysms are left axis deviation and left ventricular hypertrophy. Roentgenographically, the presence of linear calcific deposits in the ascending aorta is good evidence of syphilitic aortitis and was present in all but one case. In several instances the conventional roentgenogram also revealed calcification in the intracardiac portion of the ascending aorta and often clearly outlined the dilated aortic sinuses. Angiocardiography demonstrates the aneurysms and their effects on the neighboring cardiovascular structures.

The prognosis of syphilitic aortic sinus aneurysm is not necessarily ominous. During a five-year period of observation, two of our patients have died; three have been lost to observation; and four are alive.

ADDENDUM

Since this paper was submitted for publication, two reports from England describe operations in two patients for closure of perforated congenital aortic sinus aneurysms.[32,33]

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Ventricular Septal Defect with Aortic Incompetence Simulating Patent Ductus Arteriosus*

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ORDINARILY the diagnosis of patent ductus arteriosus in the adult is made if the patient presents with a typical continuous murmur in the pulmonary valve area, roentgen evidence of increased pulmonary blood flow, increased systemic pulse pressure, and an electrocardiogram showing either no axis shift or left axis deviation. Using these criteria, a large number of patients has been operated upon without further study and in each instance the diagnosis has been proved to be correct.

A small group of patients has recently been encountered that presented many of the signs of patent ductus arteriosus. In each instance there was roentgen evidence of increased pulmonary artery flow, and a loud left parasternal murmur strongly suggestive of a continuous murmur but actually to-and-fro in character. In addition, most of the patients showed an increase in systemic pulse pressure and a right axis shift on the electrocardiogram. Because these findings suggested an atypical patent ductus arteriosus, further diagnostic studies were carried out and demonstrated the presence of a ventricular septal defect plus some degree of pulmonary hypertension. One patient was operated upon and found to have no communication between the pulmonary artery and aorta although a prominent systolic thrill could be felt over the base of the heart. Two other patients died and autopsy findings confirmed the presence of a high ventricular septal defect with displacement and thickening of the right aortic cusp immediately above the defect, resulting in aortic incompetence. The diagnosis in the other three instances depends upon the clinical and physiologic findings.

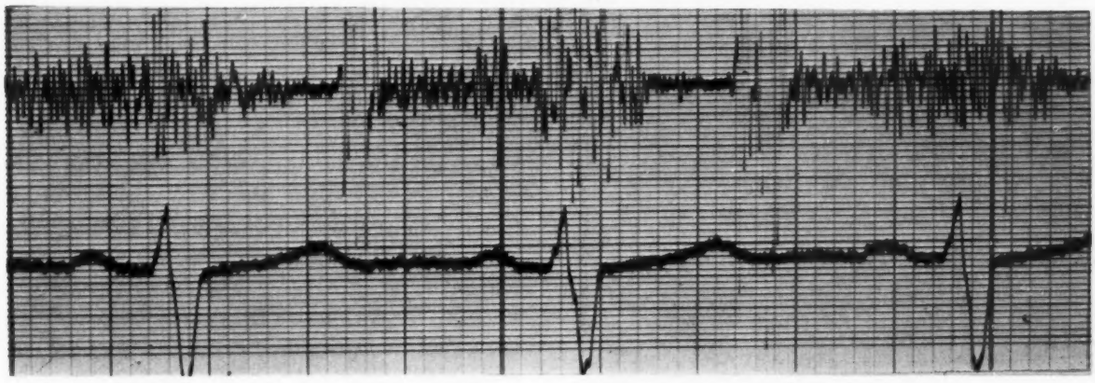

FIG. 1. Phonocardiogram showing distinct systolic and diastolic murmurs occupying most of the cardiac cycle.

Clinical and Laboratory Findings. The six patients in this group ranged in age from sixteen to fifty-one years when first studied. All of them had been known to have had cardiac murmurs

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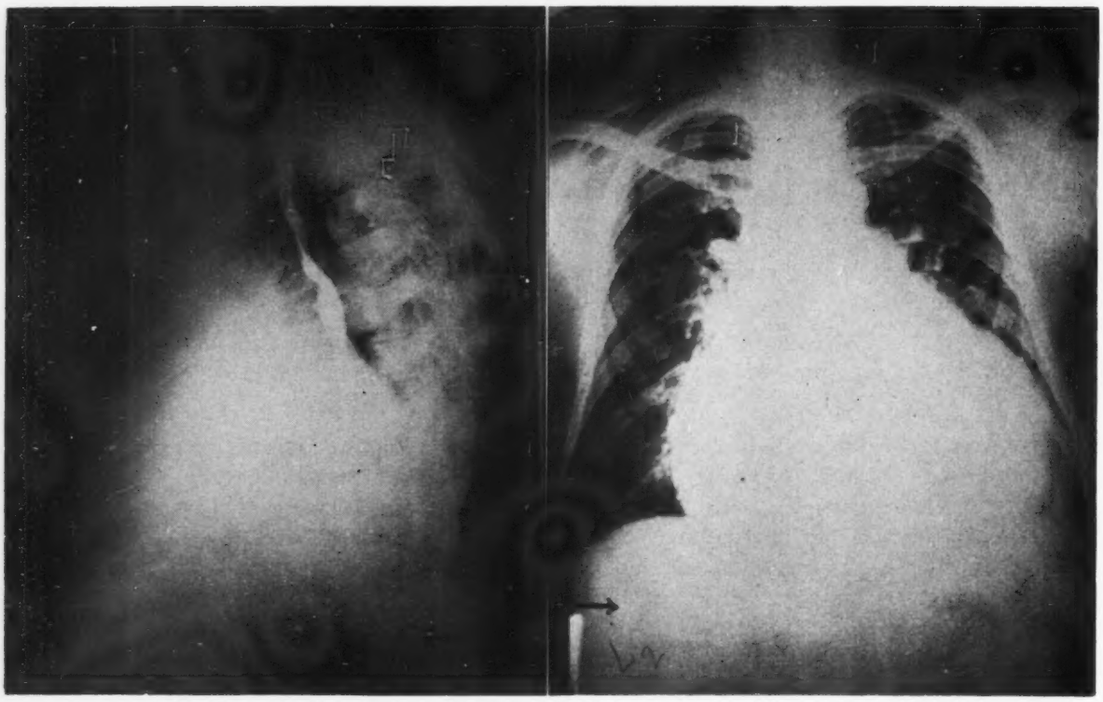

FIG. 2. Case IV. Postero-anterior and left lateral films of the chest showing cardiomegaly and prominence of the pulmonary vascular markings.

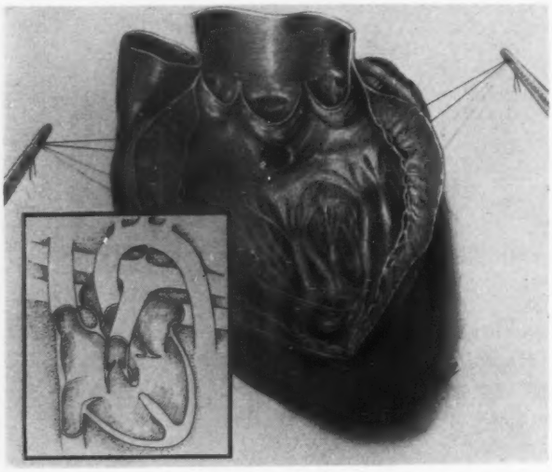

FIG. 3. Case IV. Drawing and diagram of the gross anatomic findings.

since early in life and none gave a clear-cut history of rheumatic fever. There was likewise no history of cyanosis.

On physical examination the most striking features were related to the heart. In each instance cardiomegaly was present. A loud to-and-fro murmur, often with thrill, could be heard along the left sternal border. On careful auscultation and with phonocardiography it was apparent that the murmur consisted of definite systolic and diastolic elements without obliteration of the second heart sound, although at first the resemblance to a true continuous murmur was striking. (Fig. 1.) The blood pressure was normal in two patients but in the other four there was a significant decrease in the diastolic pressure, values of 0, 20, 40 and 56 mm. of mercury being recorded. There was no evidence of cyanosis or clubbing. Various degrees of congestive heart failure were present.

No significant abnormality was found in the blood or urine. The electrocardiogram showed a right ventricular hypertrophy pattern in two cases, a right bundle branch block in two cases, a left ventricular hypertrophy pattern in one case with an associated ventricular conduction defect, and in one instance a left ventricular hypertrophy pattern. Three of the electrocardiograms showed the rhythm to be atrial fibrillation while the remainder had a normal sinus mechanism. Cardiac fluoroscopy showed considerable enlargement of the ventricles and of the pulmonary arteries suggesting a left to right shunt.

Physiologic Studies. The pertinent catheterization data are shown in Table I. Except for Case III, there is a significant increase in the oxygen

FIG. 4. Case VI. Roentgenogram of the chest showing remarkable similarity to Case IV.

content of blood in the right ventricle as compared to the right atrium, indicating a ventricular septal defect with left to right shunt. In addition, there is no significant difference between the oxygen saturations found in the right ventricle and the pulmonary artery. The one exception (Case III) was submitted to thoracotomy on the basis of the catheterization data which were suggestive of a patent ductus arteriosus, although the clinical picture was atypical and no communication between the pulmonary artery and the aorta could be found. An intense systolic thrill could be felt over the base of the heart, quite consistent with a ventricular septal defect. The error in this instance could probably have been avoided if the right ventricular sample had been taken from the outflow tract rather than from the midportion of the ventricle. The estimated shunts from left to right are given in Table I and are relatively large.

Two other points are of interest. In each instance some degree of pulmonary hypertension was present, ranging from 43/7 to 107/46 mm. Hg with an average value of 71/33 mm. Hg. In none of these cases, however, was the pressure high enough within the right ventricle to reverse the shunt and cause cyanosis, the arterial saturations all being within normal limits with an average value of 94 per cent.

FIG. 5. Case VI. Photograph showing a large defect beneath the right cusp of the aortic valve. In addition a bacterial vegetation is seen in the upper right portion of the picture.

CASE REPORTS AND AUTOPSY DATA

CASE IV. This man was first seen in 1934 when thirty-seven years old. He gave a history of dyspnea and edema in 1927 which responded to therapy. Physical examination in 1934 showed the heart to be enlarged, chiefly the left ventricle, and the blood pressure to be 148/58 mm. Hg. Very loud systolic and diastolic murmurs of a to and fro character were heard in the left parasternal region. A clinical diag-

TABLE I
CATHETERIZATION DATA

Case No. and Patient	Pulmonary Artery		Right Ventricle		Right Atrium O_2 Saturation (%)	Femoral Artery O_2 Saturation (%)	Systemic Blood Pressure (mm. Hg)	Estimated Left to Right Shunt (L./min.)
	Pressure (mm. Hg)	O_2 Saturation, (%)	Pressure (mm. Hg)	O_2 Saturation (%)				
I, J. E.	107/46	84	100/12	87	68	92	130/80	12.7
II, R. G.	65/30	81	70/0	79	58	96	160/20	7.1
III, H. C.	75/58	79	72/0	64	63	93	140/70	6.8
IV, M. LeM.	58/25	89	63/13	90	65	94	160/0	19.1
V, W. H.	42/7	86	43/0	86	77	94	140/40	7.3
VI, G. B.	80/30	83	70/0	82	61	95	168/56	12.1

nosis of patent ductus arteriosus was made. No significant abnormality was noted on the electrocardiogram.

Until June, 1953, this man lived a normal life and worked as a farm laborer. However, at that time massive edema and dyspnea developed as well as orthopnea. The blood pressure was 160/0 mm. Hg and the murmurs were as described previously, although the heart had increased tremendously in size. (Fig. 2.) There was marked distention of the neck veins and many lung rales were present. Lower extremity edema was severe and the liver was large and tender. The electrocardiogram showed a right bundle branch block. Cardiac catheterization data obtained at that time are given in Table I.

This patient was placed on a rigid cardiac failure regimen to which response was poor. He remained a cardiac invalid and died suddenly in April, 1954, at the age of fifty-seven.

Aside from the changes secondary to chronic passive congestion, the important autopsy findings were limited to the heart and lungs. The heart weighed 960 gm. Both atria were considerably dilated and the pulmonary artery was markedly enlarged. A ventricular septal defect was found high in the membranous septum immediately beneath the right cusp of the aortic valve. (Fig. 3.) The opening measured 1.5 by 0.5 cm. and the aortic cusp immediately above it was displaced inferiorly, thickened and prevented complete closure of the aortic valve. A second anomaly of great interest was an aneurysm arising in the right sinus of Valsalva. This aneurysm extended under the left cusp of the pulmonary valve and opened into the right ventricle via three small fenestrations measuring altogether about 0.6 by 0.8 cm. The coronary arteries were normal in origin and distribution. The lungs were much heavier than normal, the right weighing 570 gm. and the left 680 gm. They were spongy in consistency but floated in fixative. Considerable pulmonary congestion was present both grossly and microscopically.

CASE VI. This man was thirty-three years old at the time of death. He was found to have a heart murmur when examined in a school clinic at the age of thirteen. He did well and worked as a laborer until the age of thirty when marked congestive heart failure with anasarca developed. His initial response to therapy for congestive heart failure was good but about nine months later tachycardia and fever developed and later purpura. Examination showed the blood pressure to be 160/60 mm. Hg. The heart was massively enlarged and a loud to and fro murmur with thrill was noted in the left parasternal area. Severe congestive heart failure was present. The electrocardiogram showed atrial fibrillation and a left ventricular hypertrophy pattern. X-rays of the chest are shown in Figure 4. Cardiac catheterization studies are shown in Table I.

This man was subsequently admitted to another hospital for continuing therapy. The blood culture was positive for a coagulase-negative staphylococcus which persisted until the patient's death despite intensive antibiotic therapy.

At autopsy the more pertinent findings were in the heart which weighed 1,140 gm., most of the enlargement being present in the right ventricle. Fresh bacterial vegetations were found on the mitral and aortic leaflets. High in the membranous ventricular septum was a defect measuring 2.5 cm. in its greatest diameter. (Fig. 5.) The right aortic cusp immediately above it was markedly displaced inferiorly, thickened and prevented adequate closure of the aortic valve. The coronary arteries were normal. As in the other case, there was marked pulmonary and peripheral congestion. Microscopic examination added nothing of significance.

COMMENTS

This congenital cardiac deformity has been described in single case reports previously.[1–8] It

is also referred to in connection with an extensive series of patients operated upon for patent ductus arteriosus in which it is said to occur about once for every forty-five cases of patent ductus arteriosus.[9] It clearly is a rare disorder but it does have considerable practical significance whenever the diagnosis of patent ductus arteriosus is being considered, especially if the picture is atypical in any way.

It is apparent that the antemortem diagnosis can only be tentative since several cardiac abnormalities alone or in combination can give the same clinical and catheterization findings. The differential diagnosis must include an aneurysm of the sinus of Valsalva, as was also present in Case IV, an aortic-pulmonic window or a patent ductus arteriosus with associated pulmonary valvular insufficiency, and a simple ventricular septal defect with acquired aortic insufficiency. None of the currently available diagnostic technics can clearly differentiate these conditions.

In several of the earlier case reports the septal defect is said to be of the "Eisenmenger" type. This apparently means that the defect is in the membranous portion of the ventricular septum and does not imply that the patient has Eisenmenger's complex with a ventricular septal defect, pulmonary hypertension, a right to left shunt and cyanosis. None of the cases described have been cyanotic and the ones in this report all had normal oxygen saturation. However, all of them had some degree of pulmonary hypertension and it is entirely possible that some of them may develop enough pulmonary hypertension to reverse the interventricular shunt and develop the clinical picture of Eisenmenger's complex with aortic incompetence.

Bacterial endocarditis is an important complication of this anomaly and in at least two instances the organism has been a staphylococcus.[1] One case occurred before the antibiotic era but the one reported herein was intensively treated with numerous antibiotics without ever sterilizing the blood stream. The endocarditis in each instance involved the deformed aortic cusp or the mitral valve and not the ventricular septal defect.

Congestive heart failure seems to occur commonly in this group of cases. Until failure develops and if bacterial endocarditis does not supervene, there seems to be relatively little functional incapacity. Once congestive heart failure does occur the response to therapy seems to be poor and the prognosis is then limited. Now that it is possible in selected cases to close simple ventricular septal defects, the possibility exists that in the future surgical repair will be available provided the diagnosis can be made before an extreme degree of pulmonary hypertension develops. The usual measures employed in the prevention of bacterial endocarditis are indicated.

SUMMARY

1. High ventricular septal defect with downward displacement of an aortic cusp can closely simulate a patent ductus arteriosus.

2. Catheterization studies are very helpful in reaching a tentative diagnosis.

3. The differential diagnosis includes aneurysm of the sinus of Valsalva with rupture into the right ventricle, any communication between the pulmonary artery and aorta plus pulmonary valvular insufficiency, and simple ventricular septal defect with acquired aortic insufficiency.

4. The most common complications of this lesion include pulmonary hypertension, congestive heart failure and bacterial endocarditis.

5. This lesion may be a surgically correctible disease in the near future.

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Clinical and Pathologic Significance of Atheromatous Embolization, with Emphasis on an Etiology of Renal Hypertension*

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THE discharge from eroded atheromatous plaques of cholesterol crystals, hyaline and occasional bits of calcified debris results in a peculiar but typical alteration in affected arteries. This process, although postulated by Cruveilhier and briefly mentioned in German textbooks of pathology, has seldom been reported.[1,2] The first recent group of cases was published by Flory in 1945.[3] Two subsequent articles,[4,5] in addition to the present series of seven examples, bring the total reported instances to twenty.

Atheromatous degeneration of intimal plaques, the end stage of human arteriosclerosis—common especially in the abdominal aorta and superimposed upon syphilitic mesaortitis—represents the source of most of these emboli. The lodgment of these emboli in the medium and small arteries of diverse organs stimulates a distinctive foreign body giant cell reaction followed eventually by fibrosing endarteritis. Even though the lesions are probably frequently seen, their source and effects apparently have not been recognized and little clinical correlation has been attempted. In the present report particular emphasis will be placed on the significance of embolization of the renal arterial system.

MATERIAL AND METHODS

During routine examination of seventy consecutive cases which were autopsied six instances of cholesterol crystal embolization were identified. All tissues were formalin-fixed, cut at 5–6 micra and stained with hematoxylin and eosin. Selected sections were stained for elastic tissue utilizing the Verhoeff method, and for iron by the Gomori method.

By examining frozen sections, cut at 10 micra, with polarized light illumination, cholesterol crystals were readily identified. Modification of the Liebermann-Burchardt sterol reaction test using glacial acetic acid and concentrated sulfuric acid was applied to frozen sections. Cholesterol crystals changed from colorless to copper red and then to pale violet. The external arterial diameter was measured with a Bausch and Lomb calibrated ocular micrometer, using hematoxylin and eosin stained sections.

CASE REPORTS

Table I presents the clinical and pathologic findings of the first thirteen cases reported and the additional seven instances of this series. Table II depicts the intensity and distribution of embolization. The following cases are listed from fourteen through twenty and pertinent clinical and autopsy findings are presented when available.

CASE 14. D. M., a fifty-five year old white man, entered the hospital because of hypertension and incipient cardiac failure thirty days before his death. In 1942 a positive reaction to the serologic test for syphilis was determined and aortic dilatation was noted. The patient was given penicillin therapy. Eight months before hospitalization hypertension was observed. Following renal function studies the diagnosis of essential hypertension was made. Various combinations of antihypertensive drugs including hexamethonium, apresoline,® serpasil and nitranitol® were given but without significant lowering of blood pressure. Five months later the patient suffered a right hemiparesis and was hospitalized. Subsequent recovery of function was good. Persistent albuminuria,

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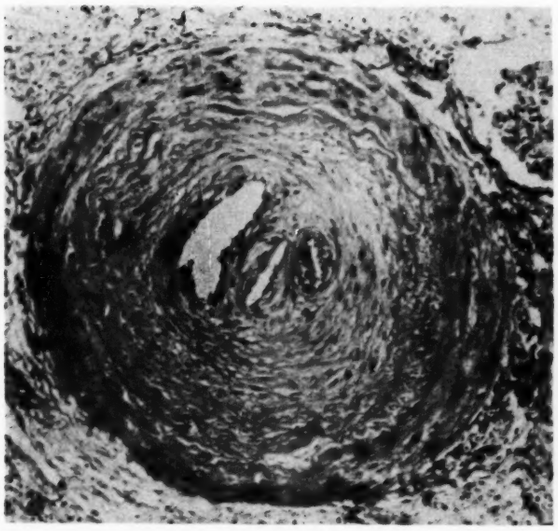

FIG. 1. Case 14. Arcuate artery of kidney, 640 micra in diameter, almost obliterated by fibrosing endarteritis with sequestered cholesterol slits; hematoxylin and eosin, original magnification × 250.

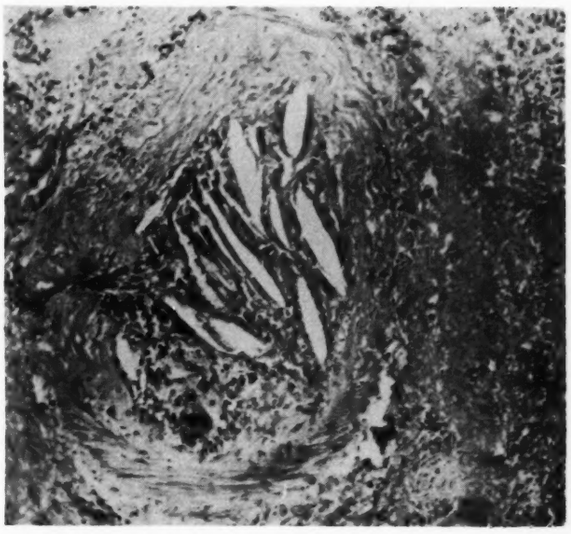

FIG. 2. Case 14. Splenic artery, 500 micra in diameter, distended by granulomatous endarteritis. Foreign body giant cells partially encircle many of the acicular spaces; hematoxylin and eosin, original magnification × 75.

microscopic hematuria, nocturnal paroxysmal dyspnea and edema of the left leg occurred during the month prior to final hospitalization.

Physical findings during the hospital stay included blood pressures ranging from 235/130 to 300/160. Funduscopic examination revealed marked nicking of veins by "silver wire" arterioles, several flame-shaped hemorrages and white exudates. The cardiolipin test for syphilis gave positive results; the results of the Kahn test were doubtful and of the Wassermann test, negative. The urine specific gravity was never above 1.010. The blood non-protein nitrogen gradually rose from 50 mg. per cent to 97 mg. per cent; terminally it was 121 mg. per cent. The benzodioxane test gave negative results and elicited a pressor response necessitating heavy sedation. Continuous intravenous administration of antihypertensive drugs failed to lower the blood pressure below 240/125. On the fifteenth day of hospitalization marked cardiac failure ensued and proved to be refractory to digitalization and mercurial diuretics.

At autopsy the ascending and descending portions of the thoracic aorta were dilated, longitudinally wrinkled, irregularly scarred in a transverse plane and presented marked atheromatous degeneration of plaques. In many places the latter were eroded and yellow grumous material, occasionally covered by fibrin, formed the aortic lining. Flat fibrous plaques and scattered small atheromatous foci covered by intact endothelium were present in the abdominal aortic segment, in contrast to the thoracic portion. The kidneys weighed 200 gm. and their capsules stripped without difficulty revealing pale, coarsely nodular cortical surfaces. The cortex varied in thickness and was often irregularly thinned, usually in a wedge-shape fashion. Other findings included bilateral pleural effusions; left ventricular cardiac hypertrophy, slight coronary arteriosclerosis; marked pulmonary congestion and edema; multiple small recent splenic infarcts; chronic cholecystitis with cholelithiasis; and two small foci of encephalomalacia in the left basal ganglion region.

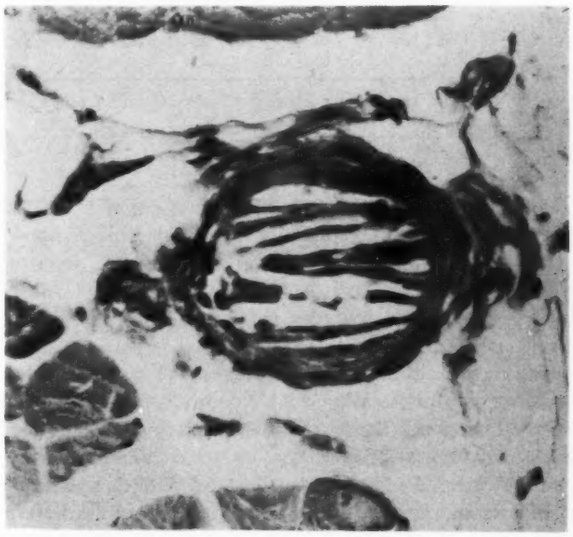

FIG. 3. Case 14. Skeletal muscle artery, 100 micra in diameter, distended by parallel cholesterol slits which are separated by large mononuclear cells. Periarterial reaction is absent; hematoxylin and eosin, original magnification × 240.

Microscopic examination of the kidney sections revealed a diffuse narrow subcapsular zone of atrophy and scattered deep wedges exhibiting a similar

TABLE 1

CLINICAL AND PATHOLOGIC DATA

Case No.*	Age and Sex	Blood Pressure	Cause of Death	Heart Weight (Gm.)	Atherosclerotic-Aortic Alterations
1	61, M	180/100	Coronary thrombosis	710	+++ abdominal
2	70, M	184/94	Cellulitis of neck	?	++ abdominal
3	58, M	?	Coronary thrombosis	?	+++ not stated
4	69, M	240/120	Pyelonephritis	?	++ not stated
5	48, M	140/80	Carcinoma of stomach	?	+++ abdominal
6	72, M	170/120	Coronary thrombosis	?	+++ not stated
7	67, M	175/100	Bronchopneumonia	?	+++ diffuse
8	69, M	130/70	Peritonitis after laparotomy	?	+++ not stated
9	50, M	160/108	Coronary thrombosis	?	+++ diffuse
10	62, M	?	Carcinoma of prostate	?	+++ diffuse
11	35, M	?	Myocardial infarct	375	+ non-eroded
12	62, M	230/130	Cerebrovascular accident	465	Syphilitic thoracic aortitis
13	67, M	225/105	Anasarca, nephrosclerosis	570	+++ throughout
14	55, M	300/160	Cardiac decompensation	480	Syphilitic, + abdominal +++ thoracic
15	53, M	204/90	Myocardial infarct	650	+++ diffuse
16	79, F	190/95	Myocardial infarct	500	+++ abdominal
17	65, M	150/100	Hemorrhagic pancreatitis	550	++ abdominal
18	67, F	160/100	Myocardial infarct	800	+++ abdominal
19	56, M	154/90	Myocardial infarct	550	+++ abdominal
20	68, M	120/65	Lymphatic leukemia	...	.....

* Cases 1 to 9 from Flory;[3] Cases 10 and 11, Zak and Elias;[5] Cases 12 and 13, Meyer;[4] Cases 14 to 20, present series.

change. The arterioles were moderately hyalinized, as were the glomeruli, especially in the atrophic regions. The arcuate, intralobular and terminal arteries ranging from 66 to 800 micra in diameter were plugged by tissue reaction consisting of foreign body giant cells encircling acicular splits. Fibrous tissue proliferation often separated the crystals from the eccentric lumens. (Fig. 1.) A collar of collagen had formed around some of these arteries, but acute inflammatory infiltration and evidence of hemorrhage were lacking. In both the spleen and pancreas numerous arteries, ranging from 66 to 600 micra in diameter, were plugged. (Fig. 2.) Vessels of adrenal, liver, thyroid, skeletal muscle, prostate and colon manifested similar occlusions by both granulomatous and fibrous endarteritis. (Fig. 3.)

CASE 15. Approximately fifteen years prior to the first hospitalization (February, 1954) this fifty-five year old white man, was told he had hypertension; dyspnea on exertion, transient ankle edema, diffuse cardiac enlargement and minimal ascites was also present. His blood pressure was 130/90. The cardiolipin test gave negative results. The serum non-protein nitrogen varied from 18 to 37 to 30 mg. per cent. Treatment with digitalis, diamox® and mercurial diuretics resulted in weight loss of thirty pounds and considerable improvement. In August, 1954, intermittent precordial pain, relieved by nitroglycerin, was noted. His final admission in September, 1954, followed more severe recurrence of the pain with no relief from nitroglycerin. The blood pressure was 204/95. The light reflex of fundal arterioles was increased but hemorrhages were absent. Electrocardiograms confirmed the impression of myocardial infarct. Two days later hypotension suddenly developed refractory to levophed®; the patient died twelve hours later.

At autopsy the heart weighed 650 gm. and presented a recent anterior septal infarction of the left ventricle. The lungs, liver and spleen were congested. The gallbladder contained many mixed calculi; the mucosa was irregularly ulcerated and the wall presented well demarcated 1–2 mm. yellow softened foci. Arteriosclerosis was generalized and of moderate intensity except in the abdominal aorta where atheromatous degeneration was marked and many of the plaques were eroded.

In multiple sections of the kidney, the intralobular and arcuate arteries measuring 66–800 micra in diameter were found to be plugged and partially occluded by cholesterol (visualized as clefts) encircled by foreign body giant cells, proliferating fibrous tissue and intimal hyperplasia. The internal elastic lamella was disrupted where the intima was hyperplastic, but collagenous replacement of media and periarterial cellular reaction were lacking. In no

TABLE II*

DISTRIBUTION AND FREQUENCY OF ARTERIAL OCCLUSIONS

Case No.†	Kidney	Spleen	Pancreas	Thyroid	Adrenals	Brain	Miscellaneous
1	++	++	+	+	0	−	−
2	+	+	+	0	−	−	−
3	+	+	+	−	−	−	−
4	0	0	+	−	0	−	−
5	+	0	0	−	−	−	−
6	0	+	+	0	−	−	−
7	0	0	+	−	−	−	−
8	0	+	0	−	0	−	−
9	0	+	+	0	−	−	−
10‡	+	+	+	0	0	?	Jejunum, rectum, prostate, common bile duct, sternum, vertebra
11‡	0	0	0	0	0	0	Heart
12‡	+	0	0	0	0	Meninges	−
13‡	+	+	0	0	0	+ encephalomalacia	Heart, stomach
14	++	+	+	+	+	Encephalomalacia	Skeletal muscle, prostate, ileum, liver
15	++	+	+	+	0	−	Bone marrow, gallbladder
16	++	+	0	0	0	0	0
17	0	0	+	0	0	Encephalomalacia	0
18	++	0	+	0	0	0	0
19	+	+	0	0	0	Encephalomalacia	0
20	−	++ splenectomy	−	−	−	−	−
Total	12	15	12	3	1		

* Symbols represent the following: 0, organ contained no occlusion; +, organ contained one or few occlusions; ++, over 10 per cent of arteries in organ were occluded; −, organ not examined histologically.

† See footnote to Table I.

‡ Degree not stated.

instance were fibrin thrombi or iron-pigmented macrophages observed. The renal parenchyma immediately adjacent to the cortex was atrophic, the tubules were small and scanty, the glomeruli were hyalinized and there was an increase of interstitial fibrous tissue and small mononuclear cells. Similar wedge-shaped atrophic zones dipped deep toward the corticomedullary junction. At the apices, arteries plugged with atheromatous emboli were usually evident. The glomeruli, although congested, showed little hyalinization away from the subcapsular regions. The arterioles were moderately hyalinized.

In the spleen, at the deepest point of a small infarct, an artery 400 micra in diameter was occluded by cholesterol embolus. A pancreatic artery (66 micra), an artery in the vertebral bone marrow (400 micra) and several arteries in the thyroid (135 to 300 micra in diameter) were affected by the emboli. In the gallbladder many arteries as large as 400 micra in diameter exhibited varying stages of reaction to the emboli. Adjacent to an intramural abscess an artery 330 micra in diameter showed giant cell reaction about the crystals, proliferating fibroblasts and loss of the internal elastic lamella. One wall of the artery had become attenuated and presented a saccular aneurysmal dilatation. (Fig. 4.) Fibrinoid necrosis of muscle and periarteritis were not seen.

CASE 16. L. V., an eighty-two year old white woman, was first admitted to the hospital for signs and symptoms of right hemiplegia nineteen months prior to her final admission. The blood pressure on four occasions prior to this episode ranged from 136/84 to 154/76; once during this period a level of 166/104 was recorded. During hospitalization a blood pressure of 190/95 was recorded but after this the levels were never above 140/80. Five months before her death the blood pressure was 154/84. While hospitalized because of severe anterior chest pain, the patient suddenly died.

The abdominal aorta was dilated and distorted by many atheromatous plaques which were often eroded, exposing grumous yellow contents. Small glistening flakes were grossly identifiable in these foci. The kidneys together weighed 200 gm. The cortical

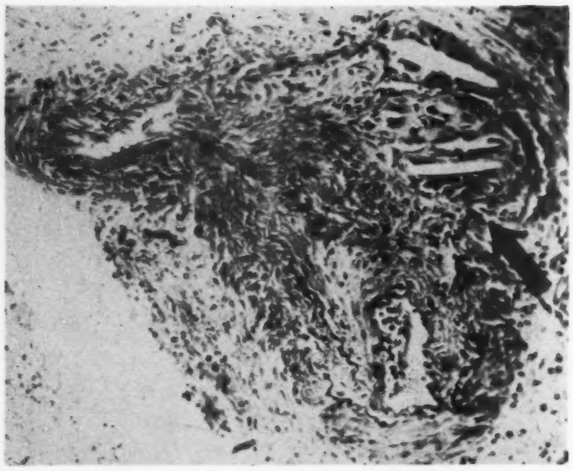

FIG. 4. Case 15. Gallbladder artery, 300 micra in diameter, with granulomatous and fibrosing endarteritis about cholesterol slits. Internal elastic lamella and media have been destroyed and a saccular aneurysm has formed (arrow); elastic tissue stain, original magnification × 100.

surfaces were finely granular and irregularly pitted by small clefts. The cortex was markedly thinned; the corticomedullary ratio was 4 to 10 mm. The peripelvic fat was markedly increased. Other findings included generalized advanced arteriosclerosis of coronary and cerebral arteries, recent and healed myocardial infarcts, cardiac hypertrophy (predominantly left ventricular) and passive hyperemia of lungs, liver and spleen. No distinct foci of encephalomalacia were encountered.

Histologically, approximately 90 per cent of the abdominal aortic wall was occupied by an eroded intimal plaque containing many acicular clefts, amorphous hyaline debris and variable degrees of recent hemorrhage. No cellular reaction occurred in or beneath the plaque. In the renal cortex, especially the subcapsular region, the glomeruli were undergoing hyalinization, the tubules were scanty and atrophic, and the interstitial tissue was unduly prominent because of increased fibrous tissue and scattered mononuclear cell infiltration. Wedge-shaped extensions of this atrophic parenchyma pointed toward the medulla, usually along arterial planes. Arcuate, interlobular and intralobular arteries ranging in diameter from 133 to 400 micra were distended and almost completely filled by cholesterol crystal emboli. The predominant phase of reaction was fibrous tissue encirclement of the crystals and sequestration from the distorted eccentric lumens. Endothelial proliferation was not marked in this phase. The less frequent cellular reaction consisted of foreign body giant cell formation around the clefts. Large mononuclear cells were plentiful among the giant cells and were occasionally seen in the media. In the spleen, several arteries 66 to 133 micra in diameter were similarly affected and for the most part in the fibrous end stage.

CASE 17. R. T., a sixty-five year old white man, was admitted to the hospital because of jaundice of five days' duration and epigastric pain lasting two days. Clinical investigation suggested acute pancreatitis and extrahepatic biliary obstruction. Hypertension of 150/100 was present, also tachycardia with numerous ventricular and auricular premature contractions. The patient had episodes of auricular fibrillation for which intensive quinidine therapy was employed. (About two years before this illness the patient had experienced a right hemiparesis from which he recovered with little residual.) The patient died suddenly seventeen days after admission, with the signs and symptoms of pulmonary embolism.

At autopsy acute hemorrhagic pancreatitis and massive pulmonary embolism were evident. Other findings included cardiac hypertrophy, moderate generalized arteriosclerosis with erosion of several abdominal atheromatous foci and 0.5 to 1.5 cm. areas of encephalomalacia affecting the cerebral cortex, brainstem and cerebellum. A solitary artery in the pancreas, 135 micra in diameter, contained a cholesterol crystal embolus. In this instance foreign body giant cells and mononuclear cells distended the lumen and encircled the long needle-like spaces. No collar of inflammatory cell reaction was localized to the artery.

CASE 18. This sixty-seven year old white woman had hypertension for at least a year before admission to the hospital. In January, 1954, the blood pressure was recorded as 135/70 and 165/80 but subsequently remained above 175/90. During the year cardiac decompensation developed, requiring digitalis and a mercurial diuretic. In December, 1954, the patient awakened with severe substernal pain, unrelieved by nitroglycerin. In the hospital the blood pressure ranged around 170/100. Electrocardiograms showed myocardial infarction and auricular fibrillation. The fasting blood sugars were elevated. The blood nonprotein nitrogen level rose from 55 mg. per cent on admission to 103 mg. per cent eight days later. The patient died on the ninth hospital day after an episode suggesting extension of the myocardial infarct.

Significant autopsy findings included advanced generalized arteriosclerosis with erosion of atheromatous plaques throughout the abdominal segment of the aorta; cardiac hypertrophy and dilatation of all chambers; recent myocardial infarct; peritoneal and pleural effusions; congestion of lungs, liver and spleen; and tubular adenomas of the kidneys. The kidneys weighed 300 gm.; the left was smaller than the right. The cortical surfaces were coarsely granular and although the corticomedullary ratio was 1 to 3, the junctions were indistinct. Foci of encephalomalacia were not identified.

Interlobular and intralobular renal arteries measuring 66 to 530 micra in diameter were occluded by cholesterol crystal emboli similar to those described previously. Cortical atrophy was moderate and usually subcapsular. In the pancreas a solitary interlobular

artery measuring 466 micra in diameter was partially filled with loose fibrous tissue sequestering cholesterol needles from the lumen.

CASE 19. R. N., a fifty-six year old man, died several minutes after hospital admission in January, 1955. At no time in the eighteen months before his death was there evidence of hypertension. The history included coronary thrombosis in 1940, a mild "heart attack" in 1947, a cerebrovascular accident with resultant left hemiplegia and slurring of speech in 1952, bursitis of the left shoulder and elbow in 1953, gastric ulcer in 1953, intermittent claudication of both legs in July, 1953, and hospitalization in June, 1954 because of superficial ulceration and cellulitis of the left great toe. A serologic test for syphilis was negative.

Gross findings included cardiac hypertrophy (550 gm.), predominantly left ventricular; advanced arteriosclerotic changes especially in the abdominal aorta; pulmonary congestion and edema; gastric peptic ulcer; and encephalomalacia of the right parietal region. The left kidney weighed 140 gm., the cortical surface was smooth except for scattered "U"-shaped depressed scars; the right kidney weighed 100 gm. The ostium of the right renal artery was narrowed by an arteriosclerotic plaque. Diffuse cortical atrophy with scattered deep scars constituted the most marked alterations. An intralobular renal artery measuring 133 micra in diameter (Fig. 5) and several splenic arteries 135 and 265 micra in diameter were occluded by cholesterol crystal emboli and resultant cellular reaction.

CASE 20. Splenectomy was performed on this sixty-eight year old white man because of acquired hemolytic anemia originating during the course of radioactive phosphorus treatment for chronic lymphatic leukemia. The blood pressure has consistently remained about 120/65 and there has been no cardiac enlargement or evidence of marked arteriosclerosis. Tests for diabetes and syphilis gave negative results.

Arteries in the spleen, ranging from 133 to 400 micra in diameter, were plugged by cholesterol emboli occasionally encircled by giant cells but usually demarcated by fibrous tissue from the lumen.

FIG. 5. Case 19. Intralobular renal artery, 133 micra in diameter, filled with cholesterol crystals separated by large mononuclear cells. Lumen is compressed and eccentric (arrow). Some adventitial fibrosis has formed; hematoxylin and eosin, original magnification × 120.

COMMENTS

The age extremes of these twenty patients were thirty-five to seventy-nine years; the majority were in the sixth and seventh decades of life. Eighteen of the patients were men. Clinical hypertension and/or cardiac hypertrophy without valvular lesions occurred in fifteen instances. Advanced coronary arteriosclerosis was present in thirteen of the twenty cases and was associated with myocardial infarction on ten occasions. Results were positive in four serologic tests for syphilis but only in Cases 12 and 14 was syphilitic aortitis diagnosed. The diagnosis of diabetes was made in two patients in the present series; none in Flory's group had diabetes and the other two authors[4,5] reporting on atheromatous embolization did not mention this disease.

An unusually high incidence of encephalomalacia (three of the five patients in this series whose cranial cavity was examined) seems noteworthy. The history of hemiplegia in Case 16 could not be correlated with histologic alterations. One of the two cases reported by Meyer[4] had similar findings and scattered cholesterol crystal emboli were identified in intracerebral arteries. A meningeal artery was occluded in his first patient, Case 12, but there was no softening of parenchyma. No such occlusions were apparent in sections of brain in the present series; perhaps they could have been demonstrated with more sections. Even though the majority of eroded plaques occurred in the abdominal aorta, the blocking of thyroid arteries indicates similar involvement of the ascending aorta and/or the carotid arteries. From these foci intracranial arteries could also be blocked and multiple small scattered areas of encephalomalacia could ensue. Of incidental

interest, in one instance (Case 11, Table 1), the embolization apparently arose from the right coronary artery and lodged in a distal portion of the same vessel.

The effect of especially severe embolization of gallbladder arteries apparent in Case 15 might be of clinical importance in isolated instances. Occlusion, spasm, granulomatous endarteritis, aneurysm formation and fibrosing endarteritis certainly can impair nutrition and function of this organ. Small infarcts, later becoming septic and suppurative, would resemble the intramural abscesses noted in this patient. Calculi were also present but the effect might have been the same even in their absence. Massive infarction of the gallbladder is usually considered pathognomonic of polyarteritis nodosa but atheromatous embolization can probably act similarly.

The first tissue responses to an embolism of atheromatous material have seldom been seen in man but were produced by Flory[3] in rabbits. Soft yellow material scraped from plaques was suspended in 5 cc. of physiologic saline. The microscopic pattern included large rhomboid cholesterol crystal plates, fat droplets and amorphous debris. Following intravenous injection of this suspension into the rabbit's ear, small pulmonary arteries were plugged by masses of red blood cells, polymorphonuclear leukocytes and large cholesterol crystals. Forty-eight hours after intracardiac injection of similar material into a rat[3] the peripheral arteries of the lung were distended by clusters of large mononuclear cells and occasional foreign body cells about cholesterol slits. Leukocyte response was scanty and no thrombi were formed.

In human cases, as exemplified in the present study, the arteries are distended and usually filled by foreign body giant cells containing long needle-like slits. The latter are readily identified as cholesterol crystals by using polarized light illumination of frozen sections. Scattered large mononuclear cells, many resembling proliferating or prominent endothelial cells, occur within the lumen. The internal elastic lamella at this stage is usually unaffected. The media and perivascular structures show no alterations. In one instance the internal elastic lamella disappeared, the media was attenuated and an aneurysm was formed. Distinct fibrin thrombi containing hemosiderin-ladened macrophages and undergoing organization are rarely encountered proximal to the occlusion. In the end stage, fibroblasts proliferate about the crystals, giant cells disappear and a lumen is re-established, but the latter is often compressed, eccentric and tortuous. The internal elastic lamella is frayed and reduplicated beneath this proliferated intimal fibrosis but the media retains normal thickness and cellularity. Adventitial fibrosis is occasionally present.

Meyer suggested that when a bolus of sharp crystals loosely bound by hyaline debris is jammed into arteries there is penetration of the intima, internal elastic lamella and even media. Spasm, which follows the arterial occlusion and penetration, pushes the cholesterol needles even deeper. The immediate cellular reaction and subsequent fibrosis are believed to be more closely related to the physical damage than to the chemical nature of the agent. Flory postulates thrombus formation about the embolus, which later recanalizes between or beside the crystals, forming slit-like vascular spaces. Distinct fibrin thrombosis with enmeshed red blood cells has not been described by Meyer and was not identified proximal to the emboli in the present group of cases. Sudden complete occlusion of the arterial lumen usually results in death of the entire tissue if the vessel represents an end artery. Such foci are seldom seen. As emphasized previously, organization of fibrin thrombus has not been noted, nor have iron-containing macrophages been identified with selective iron stains.

This surprising paucity of evidence of blood clot formation is puzzling. The most attractive explanation of the absence of clotting suggests sudden blocking of an artery capable of vigorous spasm. Following relaxation of the media, the rate of blood flow around the embolus may be rapid enough to interfere with platelet aggregation and fibrin formation. Effective inhibition of platelet aggregation by lipid-containing hyaline debris or a small amount of soluble cholesterol might also be a factor in this peculiar lack of blood clot.

Maximal occlusion as a result of the embolization may not be at the onset when spasm occurs or even later when endothelial and giant cells are plentiful, but in the healing phase. The massive proliferation of fibrous tissue produces marked narrowing of the reconstituted lumina and may gradually occlude the vessel. The large atrophic wedge-shaped zones in the kidney due to gradual replacement by fibrous tissue are more readily correlated with increasing ischemia than with healing of an infarct. If the healing phase

produces an increasing degree of renal ischemia, two results might be expected, namely, shrunken kidneys and renal hypertension. In two and possibly three cases the clinical picture suggests an abrupt rise in blood pressure from previous hypertensive levels or from normal ranges.

Could these lesions arise *in situ?* Both Flory and Meyer considered this question. Certain features of the lesions are noteworthy. The multiplicity and diversity of the affected organs and the patchy involvement of intraparenchymal arteries of varying sizes can best be explained by embolism. In the granulomatous stages the numerous large cholesterol crystals obstructing the lumen are not associated with distinctive alterations of the internal elastic lamella, media or adventitia. The mixture of granulomatous and fibrosing endarteritis in scattered vessels of the same organ would suggest that fibrosis is the end stage of this process of embolism.

SUMMARY

1. Cholesterol crystal emboli arising from eroded atheromatous plaques have been reported in thirteen patients since 1945; the present report deals with seven additional cases, bringing the total to twenty.

2. The sequence of arterial changes following lodgment of cholesterol crystal emboli includes spasm, granulomatous endarteritis, intimal fibrosis with sequestration of the cholesterol crystals, and marked diminution of lumen diameter. Tissues distal to the progressive fibrosing endarteritis become ischemic; this results in impaired function and nutrition, atrophy and, sometimes, necrosis.

3. The resulting ischemia and atrophy of the renal cortex is diffuse and marked if renal vascular lesions are plentiful. Associated clinical data suggest that activation of the renal hypertensive humoral mechanisms may ensue, as manifested by an abrupt rise in blood pressure, or intensification of existing hypertension noted in three patients of this series.

Acknowledgment: I wish to acknowledge with gratitude the generous help of Dr. Prabhunda Vanasupa. I also wish to thank Dr. H. T. Blumenthal, Director, Division of Laboratories, Jewish Hospital, for his many helpful suggestions.

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Idiopathic Pulmonary Hemosiderosis*

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Idiopathic pulmonary hemosiderosis was originally described by Virchow in 1851. The first clinical report, by Ceelen, did not appear until eighty years later, in 1931, and was followed by roentgenologic, clinical and pathologic correlations in 1944 by Waldenström.[1] An extensive review of the entire subject was published in 1948 by Wyllie, Sheldon, Bodian and Barlow.[2] Approximately thirty-three cases have been reported in the English language,[1–16] thirty of which were children and three adults. The present report concerns three adults.

Idiopathic pulmonary hemosiderosis usually starts in childhood, often in children who are sickly from birth. The disease is characterized by recurrent acute episodes of dyspnea, cyanosis, cough with hemoptysis, fever, tachycardia and anemia. Jaundice and abdominal pain occasionally are present. Anemia is often the presenting symptom and may be severe in cases with only minimal hemoptysis. The jaundice may be severe and occurs in those who have been ill for some time. Acute episodes generally last two to three days but occasionally persist for several weeks. During remission there may be apparent complete recovery, but frequently some exertional dyspnea and anemia remain. When the disease has been of long duration, cor pulmonale with congestive circulatory changes may develop. Clubbing of the fingers has been reported.

Examination of the chest during exacerbations may be unremarkable or reveal only scattered areas of dullness and rales, but some patients show signs of lobar consolidation. The appearance of the chest x-ray varies with the stage of the disease. Initially, diffuse homogeneous opacities may be seen, although at times the most dense areas are localized to the mid or central lung fields. A coarse, generalized mottled appearance is often present. As the acute phase subsides a flecked reticular pattern becomes apparent and complete clearing may ultimately occur.

In exacerbations the sputum contains hemosiderin-filled macrophages. Anemia of the iron deficiency type is present. Reticulocytosis and low serum iron are commonly found, but the response to iron therapy is variable. Serum bilirubin may be elevated, and in a few cases elevated cold agglutinin titers have been demonstrated. Measurements of the clotting mechanisms, iron metabolism and capillary fragility are within normal limits.

At autopsy the lungs are large, heavy, red-brown and firm. Microscopic examination reveals an increase in reticulum, collagen and muscle, together with decrease or fragmentation of elastic tissue in alveolar walls and small blood vessels. Fresh and old hemorrhages and many hemosiderin-filled macrophages are seen. No evidence of primary heart disease is present. Right-sided dilatation is often present in acute cases and cor pulmonale occurs if the course is protracted. One lung analysed for iron was shown to contain 1.97 mg. per 100 gm. compared to 0.03 mg. per 100 gm. in the lung of a normal control subject.

The most striking difference between the hemosiderosis seen in mitral stenosis and that in this disease is the marked vascular abnormality[25] which occurs in the former condition but is not seen associated with idiopathic pulmonary hemosiderosis.

Theories of the etiology of this disease have implicated a primary circulatory defect, a defect in elastic tissue of the blood vessels and lung, primary iron storage in the lung, tissue fragility secondary to iron deficiency and allergy. The presence of a hemolytic element has been suggested. However, the pathogenesis of the entire process has never been established.

CASE REPORTS

Case 1. (Boston Veterans Administration Hospital, No. 8832.) The patient, a twenty-five year old electrician's helper, had been in good health until one year prior to his first admission, at which time slight

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1A 1B

FIG. 1. Case 1. A, initial chest film which was interpreted as normal. Increased density in right lower lung field was thought to be due to a heavy pectoral muscle. In retrospect it is believed that it may have been caused by right lower lobe disease. B, film taken at the time of second admission, nineteen days after the first. The disease appears to involve all of the lungs except for part of the left upper lobe.

transient hoarseness and a persistent cough productive of small amounts of light yellow sputum developed. He denied all other symptoms. Three months prior to admission small flecks of blood began to appear in his sputum. A few weeks before admission the cough increased and "mouthfuls" of bright red blood began to appear. For three weeks he noted marked exertional dyspnea and a sensation of tightness at the sternal notch. One week prior to admission he had vomited twice, feeling "that something was stuck in the mid-chest." Hemoptysis had subsided just before admission. He was said to have had four chest x-rays and two examinations of the sputum alone elsewhere during the year, all of which gave "negative" results.

Physical examination revealed his temperature to be 98°F., pulse 72, and blood pressure 140/80. The patient was a well developed, slightly obese, ruddy complexioned young white man in no distress. General physical examination revealed no abnormalities.

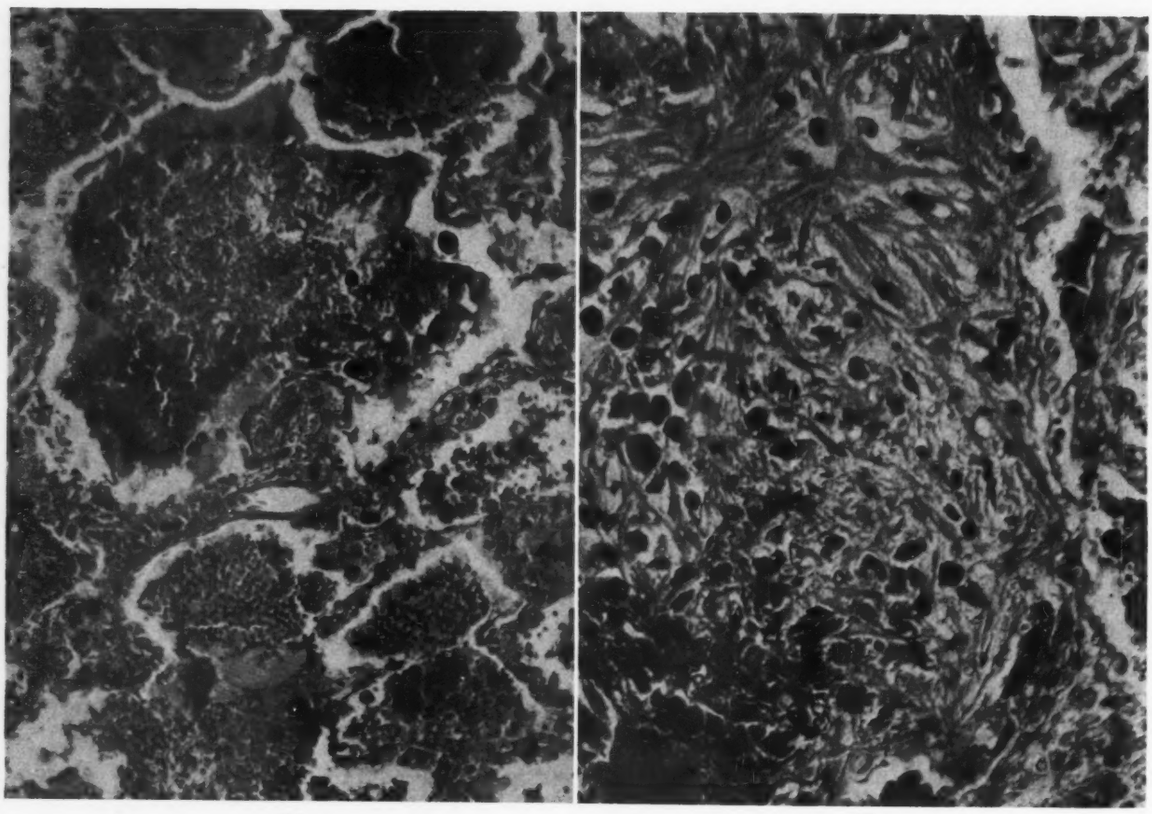
Laboratory data revealed the following: hemoglobin, on admission, 11.5 gm.; hematocrit 43 per cent; white blood count 6,500; differential count: neutrophils 54, lymphocytes 32, monocytes 1, eosinophils 3; urinalysis gave negative results; the stool guaiac test gave a negative reaction; the Kahn test gave a negative reaction; the sputum culture revealed alpha hemolytic streptococcus and Neisseria catarrhalis; sputum smears were negative for acid-fast bacilli, and the Papanicolaou smear of sputum gave negative results for neoplastic cells. Films and fluoroscopy of the chest revealed no abnormalities (Fig. 1) except for slight prominence of the pulmonary artery.

The patient was hospitalized for a total of ten days. During this period he was completely afebrile. A small amount of sputum was raised which was blood-flecked for the first few days and then the hemoptysis stopped. Laryngoscopy and bronchoscopy were within normal limits. A hemoglobin determination on the sixth hospital day was 13 gm. The patient was discharged to return in six weeks for another x-ray of the chest.

Nineteen days later the patient was readmitted to the hospital. He had been asymptomatic until three days before returning, at which time a severe shaking chill, fever, cough and dyspnea developed. He began coughing up bright red blood, the total volume being estimated at 500 to 700 cc. These symptoms persisted until admission. He received no medication at home.

At physical examination the temperature was found to be 101.6°F., pulse 136, respirations 44 and blood pressure 130/60. The patient appeared acutely ill and was moderately dyspneic. The mucous membranes were cyanotic. There was limited expansion of the chest bilaterally. Breath sounds were generally diminished, and in the region of the right lower lobe dullness, rales and bronchial breathing were noted. Small amounts of bright red blood was noted in the sputum. There were no other remarkable physical findings.

Laboratory data revealed the following: white blood count 19,500; differential count: neutrophils, 85, lymphocytes 14, monocytes 1; hemoglobin 9 gm.; hematocrit 29 per cent; urinalysis gave negative results; bleeding time was one minute; clotting time (Lee-White) eight minutes; prothrombin time 100 per cent; icterus index 10 units; blood smear revealed abundant platelets and red blood cells appeared normal; sputum smear revealed a few gram-negative



2A 2B

FIG. 2. Case 1. A, iron stain of lung showing fresh blood and siderophages (dark) in alveoli and bronchiole; original magnification × 100. B, iron stain of lung showing intra-alveolar plug of fibrous (organized) material containing many siderophages; original magnification × 200.

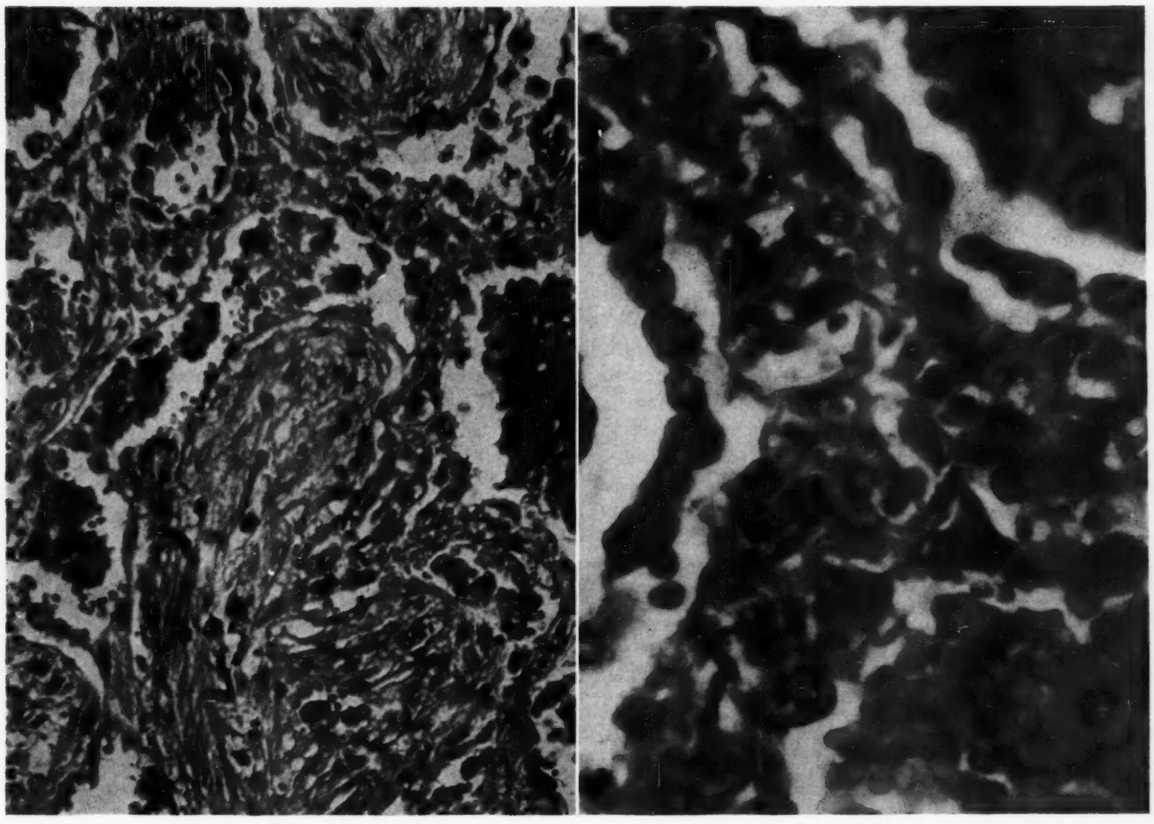
rods and gram-positive cocci; red blood cells were seen but there were few polymorphonuclears and no macrophages; sputum culture gave negative results for pathogens. Chest film (Fig. 1) showed extensive consolidation of the lower two-thirds of both lung fields, with extension of the process into the apical region on the right. The heart and great vessels were largely obscured but did not appear to be unusual.

Bedrest and oxygen therapy were instituted. Intramuscular aqueous penicillin, 300,000 units every three hours, was given. The patient received morphine and later luminal® to control his apprehension. He continued to have grossly bloody sputum while in the hospital but seemed to improve somewhat overnight. His temperature ranged between 102° to 103°F. The morning following admission the hemoglobin had dropped to 7.5 gm. with a hematocrit of 25 per cent. Through that day he received 1,000 cc. of whole blood intravenously. In the afternoon he became disoriented, then completely unresponsive. He died a few hours later after a sudden marked increase in tachypnea followed by cessation of respirations.

Permission was obtained for posthumous examination of the thorax only.

On gross examination the pleural cavities were essentially normal. The right lung weighed 1,500 gm. and the left 1,225 gm. Both lungs were quite airless and solid without discrete nodulation. Cut surfaces were meaty and dark red with a diffuse brownish tinge. Pressure caused exudation of a considerable amount of blood, but no pus was present. Red blood was present in the bronchi but their mucosa was normal. Pulmonary arteries were not remarkable. A few discrete gray-brown to black hilar lymph nodes were present, the largest being 2.5 cm. in diameter. The heart weighed 300 gm. The right ventricle was 2 to 3 mm. in thickness and the left 1.2 to 1.4 cm. No dilatation of any chamber was noted and all cardiac structures were essentially normal in appearance. The aorta and esophagus were not remarkable.

One section of each lobe of the lungs was microscopically examined. They were all at least seven-eighths airless. (Figs. 2 and 3.) The alveoli were full of red blood cells and masses of macrophages containing hemosiderin. The reaction for iron was strongly positive. The macrophages were often imbedded in plugs of organizing clot. The total area occupied by fresh blood was about twice that of older organizing material. A few neutrophils were present in or along



3A 3B

FIG. 3. Case I. A, intra-alveolar fibrous plugs; only a few of these were present; original magnification × 200. B, Verhoeff's elastic tissue stain of lung; these were the thickest alveolar walls found, showing infiltration by macrophages and lymphocytes, paucity of elastic fibers and swollen epithelial cells lining the blood-filled alveoli; original magnification × 450.

the alveolar walls where hemorrhage was fresh. There was no purulent exudate. The alveolar lining cells were found occasionally to be swollen or cuboidal and there was some thickening of alveolar walls. In a few areas alveoli were completely filled with fibrous plugs. Little hemosiderin occurred in the interstitial tissue. In each section three or four foci were found in which the alveolar walls were thickened as much as two to four times their normal thickness and contained fine collagen fibers and sparsely scattered macrophages and lymphocytes. Verhoeff's stain revealed a marked reduction of the elastic tissue in the thickened walls in some of the foci, but elsewhere the elastic tissue was essentially normal. One or two venules showed reduction or absence of elastic tissue in part of the wall but none appeared ruptured. There was no capillary engorgement as seen in mitral stenosis. Arteriolar necrosis and foreign body giant cells were absent.

The solid fibrous plugs represented old organized lesions, the dense fibrinous exudate full of siderophages was a more recent organizing process, and the fresh blood within fibrin was from very recent hemorrhage.

The hilar lymph nodes showed dilatation of the sinuses, which contained many neutrophils and littoral cells, and small numbers of red blood cells. Iron stain showed intracellular hemosiderin in the sinuses throughout the nodes. The remainder of the intrathoracic organs were not remarkable.

Cultures taken at autopsy yielded alpha hemolytic streptococcus from the heart's blood and coagulase-negative Staphylococcus aureus from one lung. Smears of the lungs were devoid of organisms.

Diagnoses were pulmonary hemosiderosis, idiopathic; hemosiderosis of hilar lymph nodes.

CASE II. (West Roxbury Veterans Administration Hospital, No. 25067.) This twenty-two year old white male college student was in good health until the age of eighteen when he coughed up a teaspoonful of bright red blood. X-ray of the chest was taken and he was hospitalized for two weeks with a diagnosis of virus pneumonia. The patient was given "sulfa" and discharged asymptomatic, the subsequent x-ray having appeared clear.

At the age of twenty-two a cough developed and the patient experienced a two-day episode of hemoptysis, bringing up six teaspoonfuls of bright red blood daily.

One month later hemoptysis recurred and persisted for ten days. Exertional dyspnea developed and the patient felt feverish. At this time he was admitted to another hospital. Positive findings included a temperature of 101.2°F., rales and bronchial breathing in the right mid-chest, and granular infiltration of the lower lung fields near the hilus. The white blood count was normal and the sputum was negative for pathogenic bacteria. The patient received intramuscular penicillin and several blood transfusions. The acute symptoms subsided in about one week. Bronchoscopy at that hospital gave negative results save for the presence of clotted blood in the main bronchi. The patient was discharged on a regimen of oral iron and referred to the West Roxbury Veterans Administration Hospital for further work-up.

On admission the patient was noted to be well developed and nourished, and without noteworthy abnormalities on physical examination.

Laboratory data revealed a hemoglobin of 10.2 gm.; red blood count 3.2 million; white blood count 5,700; differential count: neutrophils 64, lymphocytes 32, monocytes 4; urinalysis gave negative results; stool guaiac test was 1+; sedimentation rate (Wintrobe) was 11 mm. per hour; reticulocyte count 1.4 per cent; platelet count 135,000; bleeding time was four and a half minutes; venous coagulation time five minutes; the Kahn test was negative. Postero-anterior x-rays of the chest showed increased bronchovascular markings at both bases. Bronchogram was normal.

The patient was asymptomatic while in the hospital. He continued to receive oral iron. A repeat hemoglobin on the tenth hospital day was normal and he was discharged on no medication. Two weeks following discharge he noted the sudden onset of shaking chills, weakness, malaise, nausea and vomiting. Twelve hours later he began coughing up large amounts of bright red blood. Shortness of breath developed and he returned to the hospital.

At physical examination his temperature was found to be 103°F., pulse 100, respirations 24 and blood pressure 110/60. The patient appeared acutely ill and continually coughed up dark red blood. Fine rales were heard at the left lung base. Examination was otherwise not remarkable.

Laboratory data revealed a hemoglobin of 11.5 gm.; red blood count 4.1 million; hematocrit 40 per cent; white blood count 13,900; differential count: neutrophils 85; lymphocytes 14; eosinophils 1; sedimentation rate was thirty-four mm. in one hour; prothrombin time 70 per cent; bleeding time was two and a half minutes; venous coagulation time twelve minutes; reticulocyte count was 1.1 per cent; platelets abundant on smear; urinalysis gave negative results save for 1 to 3+ albuminuria; sputum culture revealed Diplococcus pneumoniae and Staphlococcus albus. Postero-anterior view of the chest showed diffuse infiltration of both lung fields and scattered residual lipiodol. Interpretation was difficult because of the presence of lipiodol.

The patient rapidly became worse. The temperature remained between 103° and 104°F., and shortness of breath became extreme. He was treated with large doses of penicillin and chloromycetin,® then aureomycin, without improvement. The hemoptysis continued and the hemoglobin dropped to 7.5 gm. The patient was transfused with 500 cc. of whole blood. Signs of acute right-sided congestive failure appeared. He was digitalized without improvement and died of respiratory failure on the third hospital day.

Autopsy was performed. On gross examination, the pleural cavities were not remarkable. The right lung weighed 1,500 gm., the left 1,440 gm. Both lungs appeared blackish red and were firm and non-crepitant. The bronchi and trachea were filled with dark blood and postmortem clot but were otherwise not remarkable. The blood vessels were of normal appearance. Cut surfaces of the lung revealed the parenchyma to be markedly engorged with blood and have a fine nodular feeling. The heart weighed 465 gm. The right ventricle was 0.4 cm. in thickness and the left 1.2 cm. The valve measurements were as follows: tricuspid valve 12 cm., pulmonic 6.5 cm., mitral 9 cm. and aortic 6 cm. The valves, musculature and arteries of the heart were entirely normal. There were no other positive gross findings.

Sections taken from all lobes, except the right middle lobe, were examined microscopically. In each the parenchyma was 75 to 90 per cent airless and 50 to 80 per cent filled with fresh blood. There were a few foci 2 to 4 mm. in diameter where alveoli were filled with an exudate consisting of old fibrin, macrophages, siderophages and fibroblasts, with occasional clumps of neutrophils. In these foci the alveolar walls and interstitial tissue were edematous with some infiltration by macrophages, lymphocytes and eosinophils. In two sections small interstitial foci of lymphocytes were noted. Occasional chronic inflammatory cells were seen in proximity to normal venules. Large, round, empty spaces were present which perhaps represented air or the former sites of iodized oil. No completely organized fibrous plugs were seen. Large numbers of siderophages were scattered throughout both the freshly hemorrhagic areas and the relatively bloodless foci, at times filling the entire alveolar space.

The section from the right middle lobe was different from the rest. Here the tissue was well aerated and many alveoli were lined with a thick eosinophilic hyaline membrane containing small hemosiderin granules and a few neutrophils. Siderophages were scattered loosely throughout but filled a few alveoli. Some alveoli contained pale edema fluid. The interstitial tissue appeared edematous with moderate infiltration by macrophages, lymphocytes, neutrophils and hemosiderin-containing macrophages. The bronchioles were empty.

Examination of sections stained with Verhoeff's stain showed elastic tissue to be preserved in hemorrhagic areas but completely lacking in the foci of organizing exudate. There was no giant cell reaction. The sinuses of the carinal lymph nodes were full of reticulo-endothelial cells and hemosiderin. These sinuses also contained lymphocytes and a few neutrophils and eosinophils. Slight vacuolization of cell cytoplasm in the lobule centers of the liver was seen and also a few polymorphonuclear cells in the adjoining sinusoids. The adrenal gland showed some reduction in cortical lipoid vacuoles. Culture of heart's blood was positive for Pseudomonas aeruginosa. Culture of the left lower lobe was positive for the same organism but there was no growth from the right lower lobe.

Diagnoses were pulmonary hemorrhage and hemosiderosis; slight chronic and subacute focal (organizing) pneumonitis; and hemosiderosis of carinal lymph nodes.

Comments. Both Cases I and II clinically fit the entity of idiopathic pulmonary hemosiderosis. The source, or sources, of hemorrhage was not discovered but there is a hint of chronic pneumonitis in Case I and it is definitely present in Case II. The latter patient received a sulfonamide in 1945 and had eosinophils in the pulmonary lesions at autopsy but no clear evidence of hypersensitivity angiitis was distinguishable; the focal lesions presumably date from his May or June episodes. That posthemorrhagic secondary infection could produce such lesions seems unlikely but must be considered a possibility.

CASE III. (West Roxbury Veterans Administration Hospital, No. 24251; Boston Veterans Administration Hospital, No. 1687.) A twenty-nine year old male office clerk was well until 1946 when he noted the onset of malaise, mild chills and a cough productive of small amounts of light green, mucoid sputum which had some blood streaking. The episode lasted two weeks and cleared spontaneously.

The patient remained asymptomatic until 1947 when symptoms recurred but now with persistent frank hemoptysis accompanied by pallor. Weakness, exertional dyspnea and palpitations were noted. He was seen by a physician, who is said to have found a hemoglobin of 50 per cent and bilateral pulmonary infiltrations on x-ray examination. The patient was hospitalized and kept at bedrest for five weeks, during which time he made a slow recovery. Two months after discharge he felt quite well and returned to his work.

In 1949 his symptoms again recurred, and he was seen at the West Roxbury Veterans Administration Hospital. Physical examination revealed a well developed, slim young male with moderate pallor. A few rales were noted at the left base.

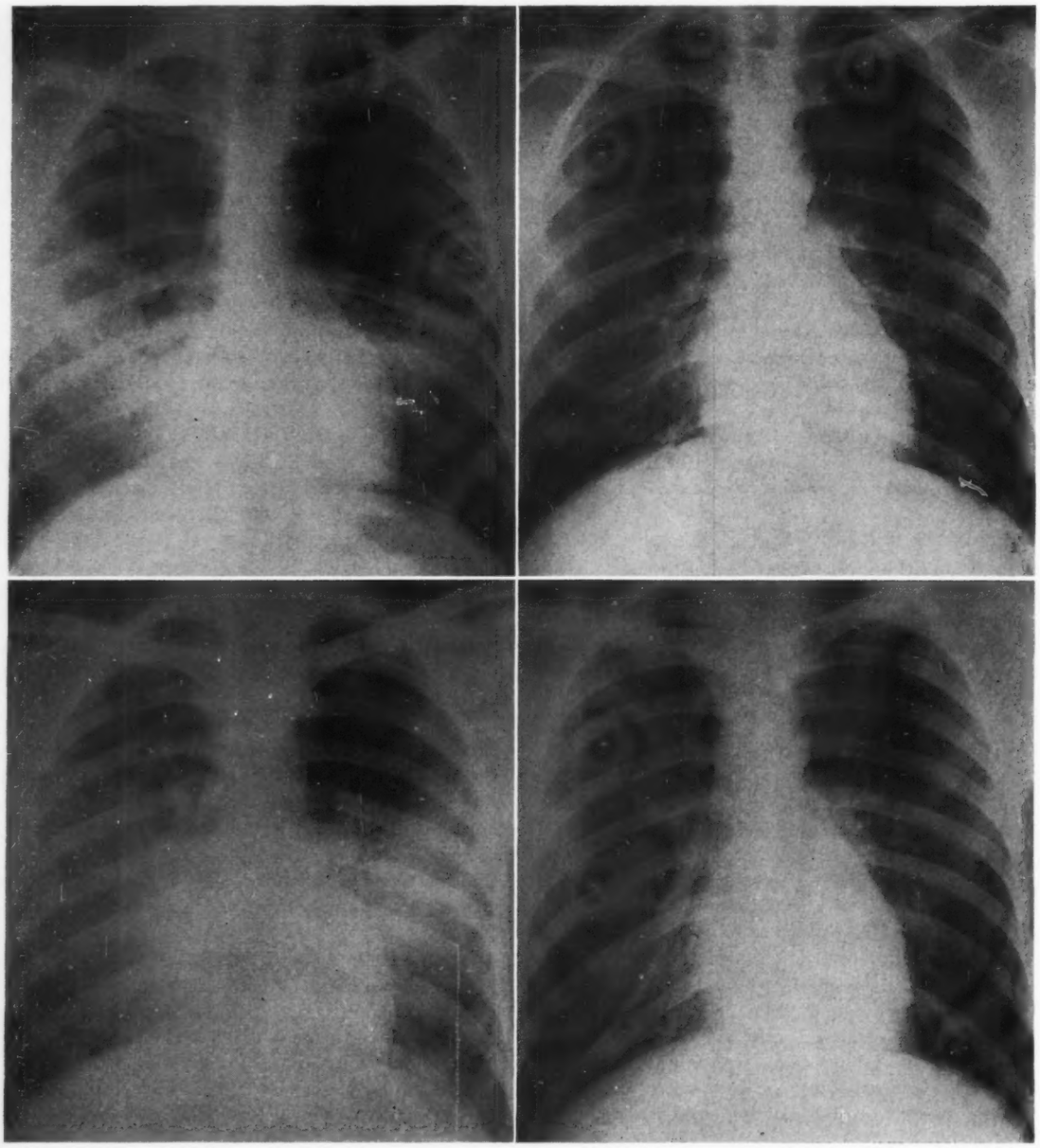
Laboratory data revealed a hemoglobin of 7.5 gm.; peripheral blood smear showed hypochromia and polychromatophilia of red cells, 2 per cent nucleated red cells and abundant platelets; white blood count was 11,700; differential count: neutrophils 55 per cent, lymphocytes 38 per cent, monocytes 4 per cent, eosinophils 2 per cent, basophils 1 per cent; reticulocyte count was 5 per cent; bleeding time was two minutes; venous coagulation time (Lee-White) three and a half minutes; prothrombin time was 100 per cent; serum bilirubin was 0.2 mg. per cent; urinalysis gave negative results for bile and urobilinogen, otherwise normal; the Kahn test was negative. Postero-anterior x-ray of chest showed diffuse miliary shadows varying from 1 to 3 mm. in diameter (Fig. 4) throughout both lung fields. Gastrointestinal series and barium enema test gave negative results. Bacteriology of the sputum, including studies for acid-fast bacilli, was not remarkable.

A diagnosis of "idiopathic pulmonary hemosiderosis" was made. The patient was given oral iron with symptomatic improvement and was discharged after three weeks. Over the next six months his hemoglobin gradually rose to 12.5 gm. and remained at that level for two and a half years. X-ray of the chest (Fig. 4) showed marked clearing within four months and within eighteen months appeared normal. The patient returned to work and felt quite well, although his friends stated that he lacked his former strength and endurance.

In 1952 a "cold" developed accompanied with a persistent dry cough. After two and a half months the cough became productive of white sputum, which soon became yellow and bloodstreaked. Ten days later chills and sweats developed, with hemoptysis of one to two teaspoonfuls of frank blood daily. Marked malaise ensued and after four days the patient was admitted to the Boston Veterans Administration Hospital.

The vital signs were normal. The patient was noted to be pale and thin but in no acute distress. General physical examination was within normal limits. X-ray of the chest (Fig. 5) revealed a finely granular infiltration involving most of both lung fields.

Laboratory data revealed a hemoglobin of 8 gm.; peripheral blood smear showed polychromatophilia of red cells and abundant platelets; white blood count was 14,250; differential count: neutrophils 76 per cent, lymphocytes 17 per cent, eosinophils 3 per cent, monocytes 4 per cent; sedimentation rate was 25 mm./hour; bleeding time was one minute; venous coagulation time six minutes; prothrombin time 74 per cent; serum non-protein nitrogen was 41 mg. per cent, total protein 5.7 gm. per cent, albumin 3.3 gm. per cent, globulin 2.4 gm. per cent; serum bilirubin was 1.6 mg. per cent; serum iron 64 gamma per cent (normal 60–130 gamma per cent); cold agglutination test, Coombs test, and stool guaiac test gave negative results; fecal urobilinogen 625 mg. per 100 gm.; (normal 30–300 mg. per 100 gm. of stool); urinalysis was entirely within normal limits; sputum smear revealed hemosiderin-filled macrophages; sputum



4A 4B

5A 5B

FIG. 4. Case III. A, initial chest film taken on June 1, 1949, showing bilateral pulmonary infiltration. B, chest film taken on October 7, 1949, four months later, showing striking clearing of lung fields.

FIG. 5. Same case. A, chest film taken on July 29, 1952, showing extensive diffuse pulmonary infiltration. B, chest film taken on September 16, 1952, seven weeks later, showing clearing of infiltration following therapy with ACTH and cortisone.

bacteriology was negative for pathogens including tubercle bacilli.

The patient had a low grade fever for the first three hospital days and was then afebrile for three weeks save for occasional temperature elevations to 100°F. During the first six weeks he continued to raise small amounts of blood and his anemia fluctuated in severity, the hemoglobin dropping as low as 5.8 gm. Bronchoscopic examination was not remarkable save for blood in the bronchi. Malaise and exertional dyspnea persisted. The patient was given four units of whole blood during this period, without reaction. After seven weeks he was started on a regimen of ACTH, 15 mg., intravenously in an eight-hour drip; two weeks later this was changed to cortisone, 100 mg. daily. While on this regimen the hemoptysis stopped; the malaise and shortness of breath diminished; and the chest x-ray (Fig. 5) showed clearing. At the time

of discharge, on his seventieth hospital day, the hemoglobin was up to 9.5 gm. Discharge medications included cortisone, 100 mg. daily, and oral iron.

The patient felt quite well following discharge but when seen one month later scleral icterus was noted and he was re-admitted to the hospital. Physical examination was unchanged except that the liver was now palpable two fingerbreadths beneath the right costal margin. Hemoglobin was 12.3 gm.; reticulocyte count 1.5 per cent. Chemical studies were consistent with serum hepatitis. The patient remained in the hospital for three weeks and the jaundice cleared promptly. X-ray of the chest at this time was normal. He was once more discharged on cortisone, iron and a high protein and carbohydrate diet.

In December he was seen again and was completely asymptomatic. Bronchograms obtained at this time were normal. Hemoglobin was 14.3 gm. All medications were stopped, and he has been asymptomatic and working daily since, but does not try any strenuous activity.

The patient has had extensive studies of his iron metabolism and blood clotting mechanisms performed in the Radioisotope Laboratories at the Boston Veterans Administration Hospital and the Hematology Laboratory at the New England Medical Center. All of the data are within normal limits and will be published at a later date.[20]

DISCUSSION

The ages of onset of symptoms in these three patients were eighteen, twenty-two and twenty-four, the ages of death in the two fatal cases were twenty-two and twenty-five. One patient is in a complete remission at the age of thirty. Family histories were non-contributory. No history of exposure to toxins was obtained. The initial symptom in each case was cough, with hemoptysis shortly thereafter. Characteristically, the course was one of remissions and exacerbations. There were some remissions to a state of apparent normal health but often exertional dyspnea and easy fatigability were present. Two patients had complete clearing of the x-ray findings during remission, while the third had clearing save for some slight residual streaking.

Acute episodes were characterized by severe cough with massive hemoptysis and shortness of breath. Areas of dullness, rales and bronchial breathing could usually be detected and cyanosis was often present. During severe attacks fever, anemia and abnormal x-rays were constant findings. In none of the patients did jaundice develop but most had reticulocytosis. All studies of bleeding and clotting mechanisms and iron metabolism were normal. There was never evidence of bleeding apart from the lungs. One patient had D. pneumoniae in his sputum but autopsy findings were not those of pneumonococcal pneumonia. No structural abnormality of the lungs could be demonstrated.

The two deaths occurred within five days of the onset of symptoms of acute exacerbation and both were due to respiratory failure. The total duration of symptoms during a single exacerbation varied from a few days to several months. Transfusions may have been of some help in one patient in whom the last exacerbation was prolonged and remission finally occurred only after ACTH and cortisone therapy. One can only speculate as to whether or not the remission was due to these drugs. There was no response to other types of therapy.

The diagnosis of idiopathic pulmonary hemosiderosis should be considered in individuals with unexplained diffuse pulmonary infiltrations and anemia. Cough with hemoptysis, dyspnea, fever and reticulocytosis may be regarded as offering further evidence in favor of the diagnosis, while the demonstration of hemosiderin-containing macrophages constitutes a strong confirmatory finding in patients free of heart disease. Aspiration lung puncture with demonstration of siderocytes in the aspirated material has been reported as a successful diagnostic measure.[26] If the patient is acutely and severely ill, jaundice may be present. Past history of similar attacks should be sought and, if the disease is of long duration, evidence of right-sided heart failure may be present. The diagnosis can be accepted only after other conditions such as mitral stenosis, infectious processes and blood dyscrasias have been ruled out.

Inasmuch as three cases have been encountered on a 150 bed medical service over a four-year period, the disease probably is not too uncommon but often goes unrecognized. It certainly must occur more frequently in young adults than is indicated in the literature. As yet no conclusive evidence has been found to explain the pathogenesis of this remarkable process. It is hoped that through recognition of the condition and further study of cases as they occur some knowledge of etiology and therapy may be gained.

In Case III there was improvement following therapy with ACTH and cortisone and, although nothing can be concluded from this single observation, these drugs merit further trial.

SUMMARY

1. A brief review of the literature, and the clinical and the pathologic picture of idiopathic pulmonary hemosiderosis is presented.

2. Three instances of this disease are reported, unusual in that they are in adults, albeit in young adults. Two cases ended fatally while the third is in apparent remission.

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Biliary Tract Studies*

I. X-ray Diffraction Analysis of Gallstones; Correlation with Occurrence of Microspheroliths in Bile

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IN the examination of bile, microscopic formed elements with a laminated, multicolored structure resembling miniature gallstones are sometimes found. These crystalline structures are known as "microspheroliths." Although such crystals have been described previously,[4,10–13,15,23,24] no mention of them was found in the American literature for the past thirty years.

This paper presents the results of a correlative study of the minute particulate content of bile and gallstones, employing microscopic examination and x-ray diffraction analysis. Microspheroliths were found in specimens from a number of the patients studied. The findings reported indicate that the presence of microspheroliths may have important diagnostic implications.

PRINCIPLES OF X-RAY DIFFRACTION ANALYSIS

When a monochromatic x-ray beam strikes a sample of a crystalline substance, a portion of the radiation is diffracted by the planes of atoms or molecules composing the substance. By means of phase re-enforcement, diffracted rays produce a series of concentric rings on a photographic film placed in their path. Figure 1 shows three such film strips after development.

The angles formed between the specimen, the axis of the incident x-ray beam, and these rings can be used to compute the lattice structure of the sample. The glancing angle θ, at which x-rays must be incident on the crystal planes in order for diffraction to occur, is related to the radiation and the crystal structure through the Bragg relation, $\sin \theta = \frac{\lambda}{2d_{hkl}}$ where λ is the x-ray wavelength and d_{hkl} is the spacing between the planes with indices hkl. The angles at which diffraction occurs and the intensities of the diffracted radiation are characteristic of a particular compound.

Only substances with a crystalline structure will cause this diffraction. Truly amorphous materials, which cannot be identified by x-ray diffraction, are extremely rare. Compounds present in amounts less than approximately 5 per cent by weight usually do not cause sufficient diffraction to be identified. The theory of x-ray diffraction and its application in biology and medicine are discussed in detail by Spiegel-Adolf and Henny.[26]

METHOD OF STUDY

Microscopy. Specimens of bile from 200 patients were studied. Bile sediment was examined microscopically for crystals in specimens obtained either directly from the gallbladder or by duodenal drainage. Gallstone fragments also were examined microscopically for their minute particulate crystalline content. Details of the procedure for obtaining and preparing duodenal drainage bile specimens for examination have been reported previously.[3] The number of crystals seen per slide (22 × 40 mm. cover glass) was estimated and recorded in the following manner: Few, less than ten crystals per slide; frequent, ten to twenty-five crystals per slide; moderate, over twenty-five crystals per slide with frequent clumps but with an average of less than one crystal per high power field.

X-ray Diffraction. Thirty gallstone specimens, obtained from twenty-two patients at operation and from eight cases at autopsy, were used in the x-ray diffraction study. Many of these were selected because either the stones or the bile from these patients were found to contain microspheroliths. Gallstones were sampled by one of two methods. When individual layers were of sufficient thickness, separate specimens were taken from each layer. Otherwise, the

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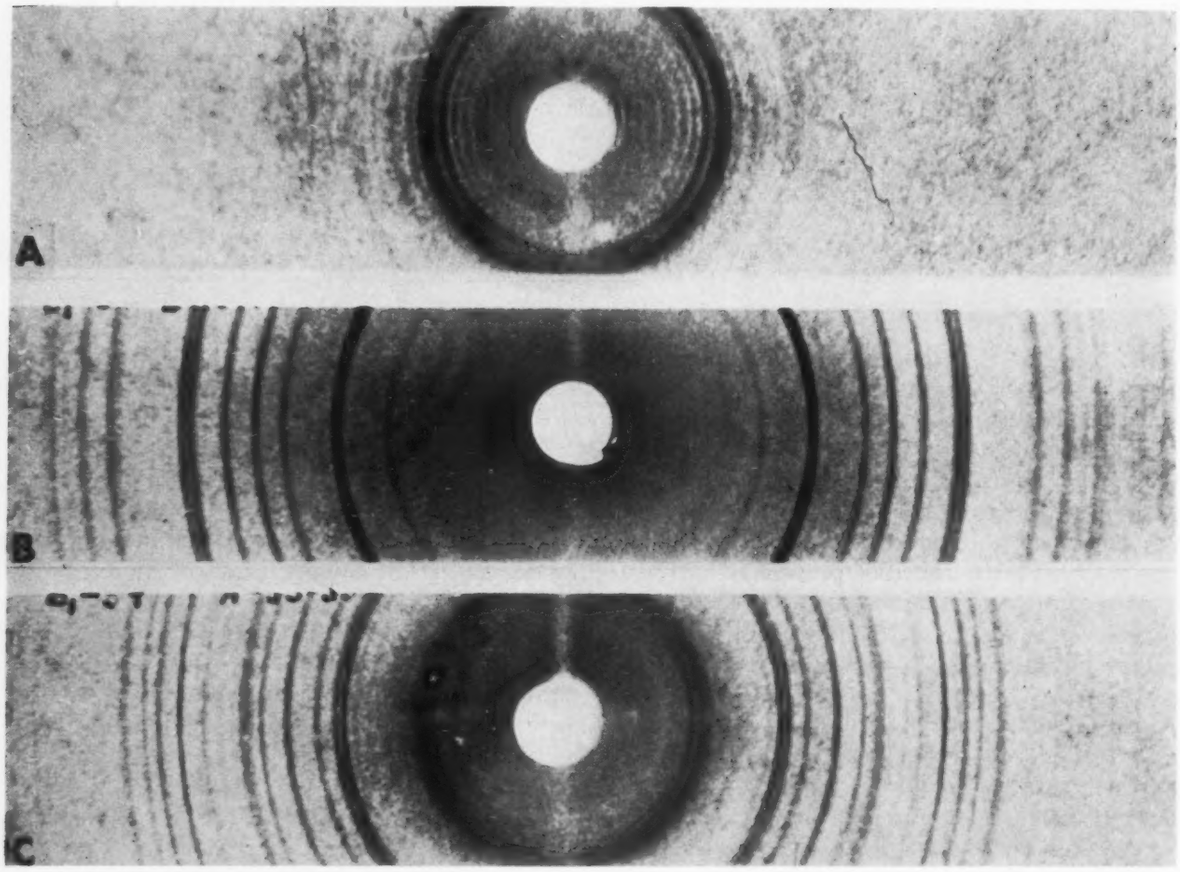

FIG. 1. Film strips showing the x-ray diffraction patterns of gallstones. A, cholesterol obtained from a sample of a "pure" cholesterol stone. B, calcite, and possibly a trace of vaterite, from a sample of a radiopaque mixed gallstone containing calcium carbonate and calcium bilirubinate. C, aragonite and cholesterol from a sample of a radiopaque gallstone containing calcium carbonate, cholesterol and calcium bilirubinate.

stones were cut in half and a single sample obtained by taking a thin cross section of the stone. In both cases the samples to be analyzed were then powdered.

The Geiger counter diffractometer, the flat-plate camera and the Debye-Scherrer methods of recording the diffraction pattern were tried. The diffractometer was discarded because of insufficient intensity in the diffraction maxima. Although the flat-plate camera resulted in increased resolution at lower angles, a correspondingly smaller portion of the diffraction pattern was recorded. The Debye-Scherrer method, using a camera of 114.6 mm. diameter, was therefore chosen as the method best suited for the purposes of this study.

Essentially monochromatic radiation was obtained by filtering x-rays from a copper target through nickel foil. Identification of the compounds present in the gallstones was accomplished by comparison of the observed directions and intensities of diffraction with published data and with patterns obtained from available samples of pure substances known to occur in bile or gallstones.

The method chosen for this study is satisfactory for identification of inorganic materials. In the case of organic substances the interplanar spacings are larger, causing the diffraction lines to be crowded together at small angles. In some cases this may have prevented detection of variations in line positions of some organic components of the gallstones.

RESULTS

Microscopic Examination. During the examination of duodenal drainage bile from 200 patients, microspheroliths were found in twenty-three of the seventy-nine patients whose bile contained cholesterol crystals, calcium bilirubinate granules or both. Microspheroliths were not found in any of the remaining 121 patients whose bile contained neither substance.

Of the twenty-three cases with microspheroliths, these were present in duodenal drainage bile in twelve while in the remaining eleven they

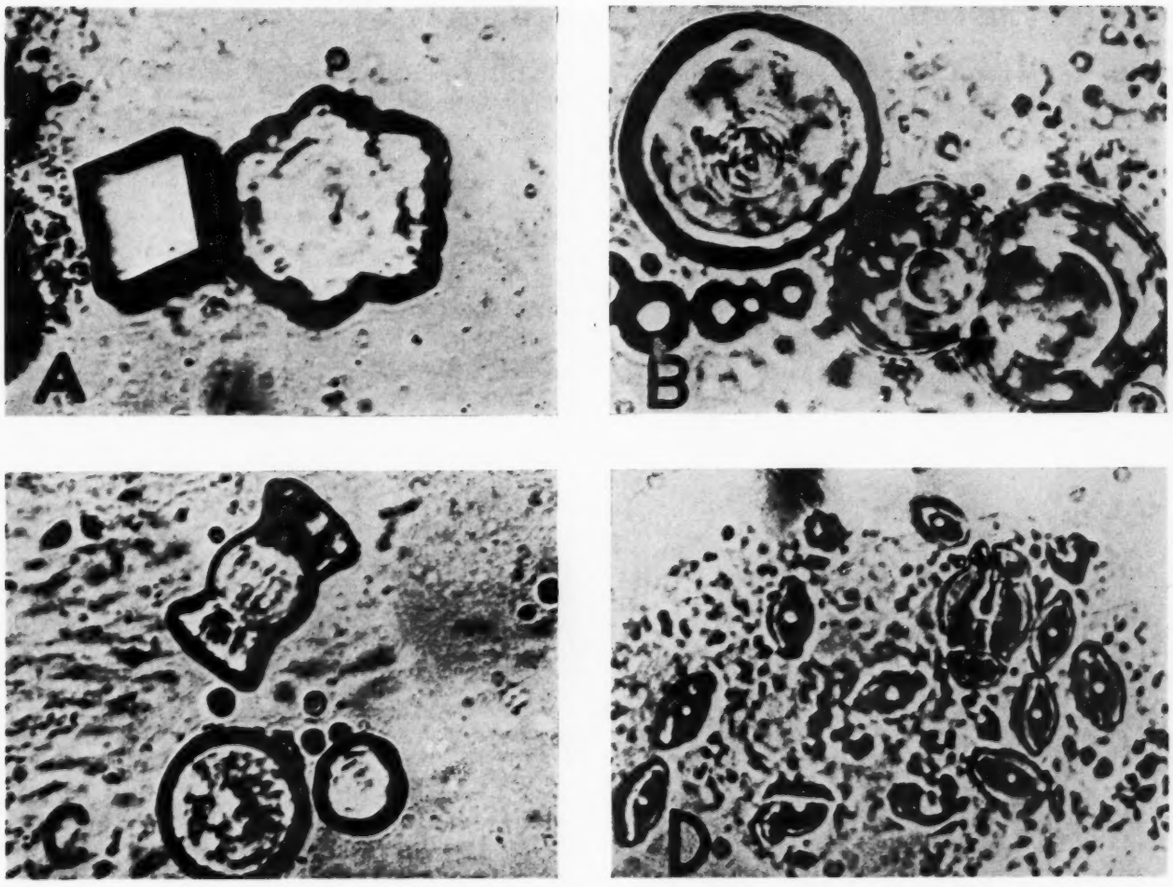

FIG. 2. Photomicrographs of various forms of microspheroliths found in bile; original magnification × 640. Although identification of compounds present in an individual crystal is not possible from this study, the most likely possibilities are indicated. A, an opaque grey multilobulated "star" crystal and a clear colorless cube—calcite. B, spherical crystals containing concentric white and yellow rings and resembling laminated gallstones—calcium bilirubinate and calcium carbonate. C, opaque grey spheres and a wheat sheaf crystal—calcium carbonate. D, green crystals resembling trichuris ova—calcium biliverdinate with some calcium carbonate.

were present in gallbladder bile only. The following diseases were found in these twenty-three patients: hemolytic anemias, four patients (one sickle-cell, one congenital and two acquired)—three patients had gallstones and the other cirrhosis of the liver; cholelithiasis without other gastrointestinal disease, nine patients (seven radiopaque, two of which were calcified*); cholelithiasis in association with other gastrointestinal disease, two patients (one associated with suppurative pancreatitis and one with liver metastases from carcinoma of the lung); cholecystitis without stone formation, six patients (one with pancreatitis and one with both calcific pancreatitis and biliary cirrhosis); cirrhosis of the liver, one patient; splenomegaly with suspected cirrhosis of the liver and suspected hemolytic anemia, one patient. Thus twenty of the twenty-three patients had gallbladder disease, fourteen with gallstones present. The other three patients had either hemolytic anemia or liver disease.

The microspheroliths in these cases appeared as single organized crystalline structures, not aggregates, varying from 7 to 50 microns in size. They were clear and colorless, or opaque and of varying shades of grey, yellow and green. Their shapes resembled those of cubes, spheres, ovoids, trichuris ova or lemons, dumbbells, wheat sheaves, clubs or multilobulated "stars." These shapes are illustrated in Figure 2. Concentric laminas, often with alternation of colors and

* Calcified, as distinguished from radiopaque, refers to the bone-like density of some gallstones which contain unusually large amounts of calcium as inorganic salts, chiefly calcium carbonate.

TABLE I

RESULTS OF MICROSCOPIC AND X-RAY DIFFRACTION ANALYSES OF BILE AND GALLSTONES FROM PATIENTS HAVING MICROSPHEROLITHS IN THEIR BILE OR GALLSTONES

Case	Crystals in Duodenal Drainage Bile*	Crystals in Gallbladder Bile*	Appearance of Gallstones	X-ray Diffraction Analysis	Remarks†
D-41	4+ chol., 4+ CaBi‡	1+ pigmented and laminated microspheroliths, 4+ chol., 4+ CaBi	Mixed stone but with some radiate chol. crystals and a sugar-like coating of crystals	Inner and outer layers—chol. and vaterite	.....
D-63	3+ CaBi	3+ pigmented and non-pigmented laminated microspheroliths	Black jackstones	Aragonite and 2 unidentified lines	Calcified gallstones
D-76	1+ CaBi, 2+ chol., 3+ non-pigmented microspheroliths	4+ CaBi, 3+ chol., 3+ pigmented and non-pigmented laminated microspheroliths	Pigment mud and small pigment stones; a single large hard stone with 3 layers—outer containing clear crystals and CaBi; middle with microspheroliths; and center of cholesterol	Outer and middle layers—vaterite, calcite and cholesterol; inner layer—cholesterol	Large gallstone was calcified
D-110	1+ CaBi, 2+ pigmented and laminated microspheroliths	4+ CaBi, 3+ pigmented and non-pigmented laminated microspheroliths	Hard, faceted and laminated stones containing 3+ pigment and microspheroliths	Calcite and possibly a trace of vaterite	Radiopaque gallstones, sickle-cell anemia
D-123	4+ chol., 3+ CaBi and 3+ pigmented and laminated microspheroliths	4+ chol., 3+ CaBi and 2+ pigmented and non-pigmented laminated microspheroliths	Faceted mixed gallstones	Cholesterol, vaterite and aragonite	.....
D-134	Pigment sand	2+ CaBi, 2+ non-pigmented laminated microspheroliths; "milk-of-calcium" bile	Amorphous brown mixed stone with large pigment content	Aragonite	Radiopaque gallstone, cystic duct obstruction
A-53-50	Autopsy case	3+ CaBi, 3+ non-pigmented microspheroliths	Faceted and laminated black stones with pigment centers	Aragonite and cholesterol	Radiopaque gallstones
D-85	1+ chol., 1+ CaBi (autopsy case)	Tarry material with 3+ CaBi and 2+ pigmented and laminated microspheroliths	Black amorphous stones containing 3+ pigmented and non-pigmented laminated microspheroliths	Aragonite	Acquired hemolytic anemia and pericholangitis
A-53-122	Autopsy case	4+ CaBi, 3+ chol., 2+ pigmented and laminated microspheroliths	Radiate cholesterol stone	Cholesterol and unidentified component	Liver metastases from cancer of the lung
A-53-147	Autopsy case	3+ CaBi, 3+ pigmented and non-pigmented laminated microspheroliths	Amorphous hard black gallstones containing pigmented and laminated microspheroliths	Aragonite	Radiopaque gallstones

* Quantitation of crystals: 1+—few; 2+—frequent; 3+—moderate numbers; 4+—innumerable.
† See text for distinction between calcified and radiopaque.
‡ Abbreviations used: chol.—cholesterol; CaBi—calcium bilirubinate.

TABLE II

RESULTS OF MICROSCOPIC AND X-RAY DIFFRACTION ANALYSES OF BILE AND GALLSTONES FROM PATIENTS NOT HAVING MICROSPHEROLITHS IN THEIR BILE OR GALLSTONES

Case	Crystals in Duodenal Drainage Bile*	Crystals in Gallbladder Bile*	Appearance of Gallstones	X-ray Diffraction Analysis	Remarks†
D-47	3+ chol.‡	4+ chol., 2+ CaBi‡	Pigment cast of gallbladder containing laminated and faceted mixed stones	Cholesterol, calcite and vaterite	.....
D-49	2+ chol.	3+ CaBi, 2+ chol.	Laminated mixed stone, large pigment content	Cholesterol	Common duct stone
D-52	3+ CaBi, 2+ chol.	Not examined	Faceted mixed stone with large chol. content	Cholesterol and vaterite	.....
D-62	4+ chol., 4+ CaBi	Not examined	Faceted amorphous mixed stone with large chol. content	Cholesterol	.....
D-82	2+ CaBi	Not examined	Amorphous mixed stone with pigment center	Amorphous material	.....
D-92	4+ chol., 1+ CaBi	4+ CaBi, 4+ chol.	Amorphous cholesterol stones with pigment center	Outer layer—chol.; inner—amorphous	.....
D-94	4+ chol., 1+ CaBi	4+ chol.	Amorphous mixed mulberry stones with pigment center	Cholesterol	.....
D-108	No bile present	4+ chol., 3+ CaBi	Mixed laminated stones	Cholesterol	Common duct obstruction, biliary cirrhosis
D-115	3+ chol.	4+ chol.	Triangular laminated mixed stones, large chol. content	Cholesterol	.....
D-116	No crystals	4+ chol., 4+ CaBi	Mixed mulberry stones	Cholesterol	.....
D-117	No crystals	1+ CaBi, 3+ chol., "milk-of-calcium" bile which was radiopaque	Laminated mixed stones, hard white outer coat on end adherent to cystic duct	Outer hard layer—hydroxyapatite; soft layer—chol.	Calcified stone, cystic duct obstruction
D-118	1+ chol.	1+ chol.; bile clear and colorless	Mixed stones with a large chol. content	Cholesterol	Cystic duct obstruction
D-130	1+ chol.	No bile present	Faceted mixed stones with pigment center	Cholesterol	.....
D-135	No bile obtained	Only clots in a fibrosed gallbladder with a perforation	Dark brown laminated stones in clot	Vaterite and unidentified lines	Common duct obstruction
A-53-82	Autopsy case	Not examined	Radiate cholesterol stone	Cholesterol	.....
A-53-108	Autopsy case	3+ chol., 1+ CaBi	Amorphous chol. sand, small amount pigment	Cholesterol	.....
A-53-140	Autopsy case	Not examined	Radiate chol. stone with pigment center	Cholesterol	.....
A-54-46	Autopsy case	Tarry mud, 4+ CaBi	Amorphous pigment stone	Amorphous material	.....
D-56	3+ chol., 2+ CaBi, 3+ octahedral crystals	4+ chol., 2+ CaBi	Radiate cholesterol stone with some pigment present	Cholesterol and 1 unidentified line	.....
D-60	3+ CaBi, 1+ chol., 1+ octahedral crystals	Not examined	Amorphous pigment stones	Amorphous material	.....

* Quantitation of crystals: 1+—few; 2+—frequent; 3+—moderate numbers; 4+—innumerable.
† See text for distinction between calcified and radiopaque.
‡ Abbreviations used: chol.—cholesterol, CaBi—calcium bilirubinate.

sometimes showing radial striae, were present in most of them. The alternately colored layers resembled a cross section of a laminated gallstone. At times the laminated crystals could be seen to fracture with cleavage planes following the striae and laminas. Optical activity was observed in many of the different forms of microspheroliths by use of polarizing filters on the microscope. Almost without exception, microspheroliths were found associated with large amounts of calcium bilirubinate granules.

X-ray Diffraction Analysis. Gallstones from ten of the patients with microspheroliths (three in duodenal drainage bile and seven only in gallbladder bile) were submitted to diffraction analysis. Data from these patients are shown in Table I. The other patients with microspheroliths either did not have gallstones or the stones were not available for examination. Data from twenty additional patients with gallstones available for study and with cholesterol crystals or calcium bilirubinate granules in their bile are recorded in Table II. The bile from two of the latter group of patients also contained clear, colorless octahedral crystals resembling calcium oxalate.

The x-ray diffraction studies showed the presence of calcium in thirteen of the thirty gallstones studied. The calcium occurred as calcium carbonate in all but one of these cases, where it occurred as hydroxyapatite. In four of these gallstones calcium carbonate was present in two of its three crystalline forms: vaterite, aragonite and calcite. In each of the other eight calcium carbonate–containing gallstones only one form of calcium carbonate was found. Aragonite and vaterite were found twice as often as calcite. Although the only substances identified by the x-ray diffraction technic were cholesterol, the three forms of calcium carbonate, and calcium in the form of hydroxyapatite, four gallstones did show one or more unidentified diffraction lines. Figure 1 shows three of the x-ray diffraction patterns obtained in this study.

The following relationships were noted when the results of the two methods of study were compared. Gallstones from nine of the ten patients with microspheroliths were found to contain calcium by x-ray diffraction analysis. Six of these stones were clinically radiopaque. The gallstones which did not contain calcium by x-ray diffraction, although microspheroliths were present in the bile, did show unidentified diffraction rings. Of the twenty patients who did not have microspheroliths in their bile, only four had gallstones containing calcium in sufficient quantity to be detected by x-ray diffraction.

DISCUSSION

Microspheroliths. One of the popular theories of gallstone formation has long been that of stone formation about a nucleus. Microliths, or very minute calculi, are of particular interest because they can represent such nuclei, and a knowledge of their chemical composition and structure might furnish clues to the mechanism of gallstone formation. Most gross gallstones consist of microliths, not only as nuclei but also apparently "cemented" together in a more or less orderly manner to form the greater portion of the stone. Fragmentation of a gallstone permits one to see these microliths under the microscope. Microliths may be simply one or more cholesterol crystals or calcium bilirubinate granules, or they may consist of substances in the form of microspheroliths. Because these microliths are usually present in the bile from patients with biliary calculi it seems probable that such microliths form in bile before gross gallstone formation occurs.

Most gallstones are composed mainly of cholesterol crystals and calcium bilirubinate granules. The appearance and significance of these two types of microliths in bile has been reported previously.[3] Microspheroliths, a third type of microlith, are so designated because of their rounded and apparent organized crystalline structure, setting them apart from simple aggregates of cholesterol crystals or of calcium bilirubinate granules. Although referred to in the earlier German literature as calcium bodies by Frerichs[7] and Naunyn,[16,17] and since described by others,[1,4,8,10–15,18] microspheroliths were first adequately illustrated and described in 1924 by Rous, McMaster and Drury.[23,24]

Qualitative microchemical studies of microspheroliths by Martennson[15] and by Rous et al.[23,24] demonstrated the probable presence of calcium carbonate, calcium-pigment complexes, an inorganic scaffolding and possibly traces of cholesterol.

We have been unable to find any published data of studies utilizing the x-ray diffraction technic as a means of determining the composition of microspheroliths. The x-ray diffraction method is unique because it permits determination not only of the chemical compounds present but also of their crystalline forms. Such deter-

minations by chemical methods are exceedingly difficult, especially when one is dealing with small amounts of mixtures containing several types of crystals.

X-ray diffraction analysis of the gallstones from the ten patients with microspheroliths in our series showed the presence of calcium carbonate in nine instances. The gallstone from the tenth case was found to contain only cholesterol and unidentified diffraction lines by x-ray analysis, although it is possible that calcium carbonate could have been present in an amount of less than 5 per cent by weight and not have been detected. Calcium carbonate, sulfate or oxalate crystals are known to occur frequently in urine sediment in shapes resembling some of the non-pigmented spherical and dumbbell-shaped microspheroliths found in bile. These findings suggest that microspheroliths contain the various calcium salts identified in gallstones by our x-ray diffraction studies, as well as those of others.[6,9,19–21,25] The occurrence of a slightly pigmented radiate cholesterol gallstone in the patient with microspheroliths but without detectable calcium carbonate in the stone suggests that cholesterol also may be a component of microspheroliths.

Although calcium bilirubinate cannot be identified in the human bile by x-ray diffraction because of its amorphous state, the work of Martennson[15] and of Rous et al.[23,24] indicates that this pigment is the substance responsible for the pigmented rings seen in some microspheroliths. Variations in color from yellow to green or brown may be due to oxidation of calcium bilirubinate, resulting in the formation of calcium biliverdinate or other oxidation products.

Although the cause of microspherolith formation is obscure, the nature of their occurrence suggests several possible factors: (1) increased calcium concentration in bile, (2) increased excretion of biliary pigments by the liver, and (3) qualitative or quantitative changes in other biliary constituents which affect the solubility of calcium in bile.

There is no evidence of increased calcium excretion in hepatic bile in patients with cholelithiasis. Because of the association of microspheroliths with gallstones containing large amounts of calcium, and because the gallbladder bile in some of these cases contains increased amounts of calcium, this increase occasionally may be a factor in microspherolith formation. However, the inconsistency of this increased calcium content of gallbladder bile, and the fact that microspheroliths can be found in hepatic bile in the absence of a gallbladder, demonstrates that other factors also are present.

These other factors might be the protein content, pH, or concentration of anions which can form insoluble compounds with calcium. The association of liver disease with microspheroliths by others,[1,4,10–13,23,24] as well as in one of our cases, suggests that an abnormal bile unable to retain calcium in solution may result from liver disease.

Patients with hemolytic anemias have increased biliary pigment excretion and an increased incidence of gallstones of the pigment variety. Although the number of such gallstones which we have examined is small, all have contained large numbers of pigmented microspheroliths. This leads us to assume that increased biliary pigment excretion can be a chief cause of microspherolith formation in certain cases.

X-ray Diffraction. Relatively few reports of studies of gallstones utilizing x-ray diffraction are available. To date such studies have shown the presence of the following substances: cholesterol, calcium bilirubinate, calcium-copper bilirubinate, calcium carbonate, and calcium phosphate.[6,9,19–22,25,27]

Cholesterol may be in microcrystalline or macrocrystalline forms, the former being more prominent in "mixed" stones, the latter in the "pure" type of cholesterol stone.[9,22,27]

Calcium bilirubinate has been found in the crystalline form (as well as in the amorphous) only in gallstones from cattle.[6] Pigment in human gallstones studied by the x-ray diffraction technic has always been found in the amorphous form, never the crystalline.[25] In our series an x-ray diffraction pattern which could be attributed to biliary pigment was not found in any of the twenty-five gallstones which contained large amounts of pigment. The complete absence of any diffraction pattern in two of these gallstones, which were of the "pure" pigment type, indicated that amorphous material formed at least 95 per cent of each stone. Microscopic examination of fragments of these stones showed them to be composed chiefly of calcium bilirubinate granules. For these reasons the x-ray method has not been helpful in identifying the pigment content of gallstones. Consequently, demonstration of typical pigment granules microscopically is at present the most practical, although not the

most accurate, method of confirming the presence of calcium-pigment granules in gallstones or bile.

Calcium carbonate, particularly in radiopaque gallstones, was found in its three crystalline forms: aragonite, vaterite and calcite.[6,9,19–21] On occasion, gallstones were found to contain calcium phosphate and calcium carbonate combined in mineral forms resembling apatite or dahlite.[19,20,25] Twelve of the gallstones in our series were found to contain one or more forms of calcium carbonate, while an additional gallstone contained hydroxyapatite. "Milk-of-calcium" bile contained calcium carbonate as calcite and aragonite,[20] while the "porcelain" gallbladder wall contained chiefly calcium phosphate.[21] Oxalic acid or a "similar crystalline substance" was reported in the outer layers of some gallstones.[5]

CONCLUSIONS

Microspheroliths have been found associated with radiopaque gallstones, with the pigment gallstones occurring in hemolytic anemias, and in persons in whom liver disease was the only demonstrable gastrointestinal disturbance. Although the precise mechanisms of microspherolith formation are unknown, the data presented indicate that increased calcium concentration in gallbladder bile, increased pigment excretion in hepatic bile, and unknown changes in hepatic bile composition probably are responsible for microspherolith formation. Additional evidence that calcium carbonate is one of the components of microspheroliths is presented. Calcium-pigment complexes form a second important constituent of microspheroliths, and cholesterol may be a third component.

The presence of microspheroliths in duodenal drainage bile indicates that a "stone-forming" state exists within the biliary tract and that gallstones containing large quantities of calcium are either present or forming.

SUMMARY

The results of x-ray diffraction analysis of gallstones from thirty patients are reported. Microspheroliths found in bile or gallstone fragments from twenty-three of the 200 patients studied are described. Microscopic examination of bile and gallstone fragments, together with the x-ray diffraction studies of gallstones, indicates that some of these microspheroliths contain calcium, usually in the form of calcium carbonate. The presence of such crystals in duodenal drainage bile suggests the presence of calcium-containing gallstones. The possibility of a hemolytic anemia should be considered if large numbers of pigmented microspheroliths are found.

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Therapy of the Malignant Lymphomas*

I. A Study of 116 Cases

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UNTIL the nature of lymphomas is known therapy will be more empirical than rational. Consequently, as methods of therapy appear, there must be a constant re-evaluation of the results of treatment. Of the agents now in use only roentgen radiation has been well evaluated. Many patients have been treated with nitrogen mustard but two major deficiencies in the reports of its use have been noted: (1) The follow-up has been too short, and (2) experience has been only with relatively unfavorable cases. The majority of reported cases treated with nitrogen mustard have been patients who had long-standing disease resistant to other therapy or patients who had not been treated previously but who had extensive disease when first seen. Prognosis in both groups is poor. Although the information gained from this type of case has been valuable, complete evaluation must come from experience with all stages and types of lymphomas.

In the present study we are attempting to extend evaluation of the effectiveness of nitrogen mustard by reporting cases of patients treated solely by nitrogen mustard and followed for periods up to six years. We also present data to indicate to what degree the addition of nitrogen mustard has changed the prognosis of lymphoma and to define further the relationship between nitrogen mustard and other methods of treatments.

METHODS

All patients with malignant lymphoma who were first treated in the Albany Hospital between January 1940 and December 1950 were included in the study. No patients were added after the latter date, but patients were followed to July 1, 1953. The total number of patients was 116. Two additional patients had clinical manifestations of lymphoma and were so treated but there was no histologic confirmation and no data are included on these two. We have excluded six other patients who were treated during this period but were first treated prior to it. The biopsy or autopsy slides were reviewed in ninety cases by two persons working independently and without knowledge of previous diagnosis or of the course of the patient. Because of frequent conflicts of opinion, additional opinions were sought from the Department of Pathology. In four additional cases detailed descriptions of the histologic appearance of the tissue were available. In the remaining twenty-two cases the diagnosis was made by biopsy but slides could not be located for review.

The cases were subdivided into Hodgkin's disease, lymphosarcoma, follicle lymphoma and reticulum cell sarcoma. The classification is based on that of Gall and Mallory but with combination of some groups. The stem cell and clasmatocytic lymphomas were combined as reticulum cell sarcoma. The two types of lymphocytic tumor were combined under lymphosarcoma, and the two types of Hodgkin's disease were not separated. All leukemias were excluded. In a subsequent report the findings will be given for each subgroup but for the present report it did not appear necessary to consider the seven groups separately.

All cases were followed to the time of death or to the end of the study. In those instances in which patients were subsequently treated elsewhere details of treatment and results were obtained. The majority of the patients were not seen by the authors but the information was obtained from the records.

Roentgenotherapy was not entirely uniform throughout but treatment methods were basically similar. At the Albany Hospital from 1940 to 1950 the source of radiation was from a 200 kv. unit with added filtration of 1.5 mm. of copper and 1 mm. of aluminum. The target-to-skin distance was 50 cm. Fractional doses of 100 to 250 r in air were given to a total of up to 2,500 r in a single area. In certain areas such as the chest or abdomen multiple portals were used with a dosage up to 2,000 r to each portal. Local disease was treated more vigorously than generalized disease. Additional treatment was given to areas where there were recurrences and when new disease appeared. Prophylactic treatment and total body radiation were not used.

Nitrogen mustard was given in a dose of 0.1 mg. per kg. of body weight daily for four days. The only nitrogen mustard used was methylbis (beta-chloroethyl)

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TABLE I

NUMBER OF CASES RECEIVING EACH TYPE OF THERAPY

Type of Lymphoma	X-ray Only	HN_2 Only	X-ray Followed by HN_2	HN_2 Followed by X-ray	Surgery Only	None
Hodgkin's disease	31	6*	17	7	3	1
Lymphosarcoma	16	6	8	3	1	5
Follicle lymphoma	3	2	1	1	0	0
Reticulum cell sarcoma	2	1	0	0	0	1

* One patient with miliary tuberculosis and lymphoma who received HN_2 is excluded.

amine hydrochloride (HN_2). Selection of cases for nitrogen mustard therapy was not impartial. Patients so treated either had extensive, symptomatic disease or were refractory to previous therapy. None had localized disease. Three patients received triethylene melamine (TEM) after prior treatment with roentgenotherapy or HN_2. For purposes of this report these are included under nitrogen mustard therapy. Supportive measures were given as needed and in most cases were needed when the patients no longer responded to other therapy.

Several patients were treated with roentgenotherapy until this no longer seemed suitable and were then given HN_2. Others were given HN_2 initially and later in the course of their disease received roentgenotherapy. For the most part the agent used initially was the principal agent for the patient. On five occasions patients received both forms of treatment simultaneously; these are indicated in the tables. The period of remission has been calculated after each course of therapy and after the total remission. This was the period during which the patient was asymptomatic or had symptoms that did not prohibit his usual daily activities, whether or not objective evidence of disease was present. This is more difficult to calculate than survival time but in these conditions may be a more significant measure of therapy. Survival times have also been calculated and are more or less in proportion to the figures for remission. This has been done so that these results can be compared with those of others.

Table I lists the number of cases receiving each type of therapy.

SURGERY

Hodgkin's Disease. Three patients, two with disease localized to cervical nodes, were treated by local excision. (Only those patients in whom all obvious diseased tissue was removed and no other therapy given are considered herein to have been treated surgically.) A patient who had tumor removed from the spinal canal died within one month. Of the two patients with cervical node disease one was without recurrence twelve years later and the other, also in remission, was treated with roentgenotherapy after a recurrence eight years after the initial lesion was removed.

The excellent results obtained by removal of the few enlarged nodes in two of the patients cannot be used as evidence for the effectiveness of surgery in such instances. The surgical procedure was no more extensive than at biopsy of many patients who do poorly even with additional treatment. The long survival of these two patients is probably a consequence of the relatively benign nature of their disease and not of the treatment.

Other Lymphomas. Only one patient with lymphosarcoma was treated by surgery alone. This patient died three days following resection of a lesion in the small intestine.

ROENTGENOTHERAPY

Hodgkin's Disease. Thirty-one patients were treated with roentgenotherapy alone. An additional seventeen patients received roentgenotherapy initially; this formed the major therapy, but they also received HN_2 later in the course of the disease. (Table II.) In these forty-eight patients posttreatment survival and total remission ranged from 0 to 125+ months. Sixty-two per cent survived one year, 39 per cent two years, 35 per cent three years and 18 per cent five years. Great variation in individual responses was noted. Some patients had long remissions, up to 93+ months, without recurrence. Others had good initial response with progressively shorter remissions from subsequent courses of roentgenotherapy. Fourteen patients (29 per cent) did not show a response of a degree sufficient to be classified as remission.

A wide variation occurred in the duration of disease and the amount of treatment received

TABLE II

HODGKIN'S DISEASE

Patient No.	Sex and Age	Extent of Disease[1]	Condition[2]	Duration Prior to Therapy (mo.)	Months Remission[3] Each Course of Therapy									Duration of Remission (mo.)			Survival Time (mo.)	
					1	2	3	4	5	6	7	8	9	Total	From X-ray	From HN_2	Total	After Therapy
Roentgenotherapy Only																		
107	M, 24	II	G	3	2	122+									125+		128+	125+
1	M, 66	I	G	1	12	3	3	2	93+						113+		114+	113+
123	M, 22	II	G	4	34	77+									111+		115+	111+
116	M, 23	V	P	1	93+										93+		94+	93+
52	F, 69	II	F	12	6	52									58		70	58
117	F, 27	II	F	25	48	0									48		82	57
34	F, 53	III	G	35	36	8									44		88	53
147	M, 39	I	G	1	40+										40+		41+	40+
36	M, 44	II	G	3	21	0									21		28	25
115	F, 43	II	G	12	14	0	0								14		32	20
101	M, 45	I	G	3	7	6									14		20	17
32	M, 56	II	G	22	11	0									11		37	15
108	F, 51	II	F	6	4	4	0								8		14	8
40	M, 17	V	F	8	8	0	0								8		24	16
102	M, 27	I	G	0	7	0									7		15	15
118	F, 26	V	F	3	3	2	0								5		11	8
112	M, 41	III	G	21	3										3		26	5
110	M, 44	II	F	7	2	0	0								2		11	4
4	F, 53	I	F	6	2	0	0	0							2		9	3
114	M, 51	V	G	0	0	0									0		14	14
24	M, 26	I	G	18	0										0		30	12
119	M, 27	II	F	5	0	0									0		16	11
37	M, 9	III	F	9	0	0									0		18	9
111	M, 44	I	F	24	0										0		30	6
142	F, 74	V	F	4	0										0		9	5
10	M, 38	II	F	12	0										0		15	3
121	M, 37	II	G	3	0										0		6	3
122	M, 57	II	F	6	0										0		8	2
41	M, 16	II	G	8	0										0		9	1
120	F, 75	V	F	2	0										0		3	0
105	M, 53	V	P	2	0										0		2	0
Roentgenotherapy Initially—HN_2 Later																		
78	F, 30	V	F	2	14	9	7	7	3	12	2	1	3					
					6T	2	1T	2	2	0	0			71	63	8T	79	77
103	M, 29	I	G	24	45	19	2	0						66	64	2	92	68
33	M, 22	I	G	0	6	10	6	5	8	18	2	3	7					
					0	0	0	0						64	64	0	71	71
22	M, 31	II	F	3	36	3	8	1	3	2	4	2		59	56	3	66	63
6	F, 24	II	G	4	22	14	2	4	6	6	0			54	44	10	66	62
27	F, 44	II	G	14	4	6	6	16	15	0				47	31	16	66	52
23	M, 22	II	G	3	30	2	7	2	1	2	0			44	30	14	49	46
38	F, 27	III	P	9	6	7	3	2	5	5	2	6	0	37	29	8	48	39
17	M, 55	II	..	2	29	3	0							32	32	0	40	38
12	F, 19	II	F	7	2	2	3	7	2	0	0	0		16	14	2	31	24
2	F, 70	II	G	2	8	4	4	0						16	8	8	21	19
9	M, 63	I	G	5	12	4								16	12	4	21	16
25	M, 18	II	G	8	5	2	0	0	0					7	7	0	23	15
76	F, 55	I	G	3	3	2	0							5	3	2	13	10
65	M, 48	II	G	4	4	0	0	0						4	4	0	11	7
21	M, 18	II	G	30	0	0	0	0						0	0	0	46	16
18	M, 41	III	..	12	0	0								0	0	0	16	4

TABLE II (*Continued*)

Patient No.	Sex and Age	Extent of Disease[1]	Condition[2]	Duration Prior to Therapy (mo.)	Months Remission[3] Each Course of Therapy									Duration of Remission (mo.)			Survival Time (mo.)	
					1	2	3	4	5	6	7	8	9	Total	From X-ray	From HN_2	Total	After Therapy
HN_2 Only																		
39	F, 44	III	G	1	75+	.....	.....	..	.....	..	..	..	..	.....	.....	75+	76+	75+
54	M, 44	II	F	5	$\overline{52}$+	.....	.....	..	.....	..	..	..	..	.....	.....	52+	57+	52+
16	F, 47	V	G	..	$\overline{10}$*	4	4	3	0	$\underline{2}$	..	..	..	.....	.....	13	.....	25
13	M, 57	II	F	60	1	$\overline{4}$	$\overline{4}$	$\overline{5}$	$\underline{0}$	..	..	..	..	.....	.....	14	86	26
5	M, 39	II	G	5	$\overline{4}$	$\underline{5}$	$\underline{2}$	$\underline{0}$	$\underline{0}$	..	..	..	..	.....	.....	11	17	12
29	F, 57	V	F	27	$\underline{1}$	.....	.....	..	.....	..	..	..	..	.....	.....	1	29	2
HN_2 Initially—Roentgenotherapy Later																		
15	F, 36	II	G	3	$\overline{4}$	$\underline{5}$	$\underline{3}$	$\underline{2}$	$\underline{1}$	$\underline{4}$	$\underline{5}$	2	$\underline{1}$	.....	.....	....	.....	.....
					$\overline{4}$	$\overline{1}$	$\overline{4}$**	$\underline{0}$	.....	..	..	..	..	36	5	31	42	39
26	M, 15	II	G	25	$\overline{5}$	4	3	$\overline{3}$	0	..	..	..	..	15	0	15	43	18
62	M, 47	III	F	6	$\overline{9}$	$\overline{2}$	$\underline{0}$	$\underline{0}$	.....	..	..	..	..	11	0	11	21	15
75	M, 44	II	G	8	$\overline{2}$	$\overline{6}$	$\underline{0}$	$\underline{0}$	.....	..	..	..	..	8	6	2	19	11
53	M, 67	III	..	58	$\overline{3}$	1	$\overline{2}$	0	.....	..	..	..	..	6	2	4	71	13
7	M, 31	V	F	13	$\underline{0}$	$\underline{0}$	$\underline{0}$	..	.....	..	..	..	..	0	0	0	25	12
28	M, 32	V	G	1	$\underline{0}$	$\underline{0}$	$\underline{0}$	$\underline{0}$	0	..	..	..	..	0	0	0	10	9
Surgery Only																		
109	M, 7	I	G	6	146*+	.....	.....	..	.....	..	..	..	..	146+	.....	....	152+	146+
113	M, 6	I	G	12	98*	5+	.....	..	.....	..	..	..	..	103+	5+	....	115+	103+
139	M, 65	V	P	1	0*									0	.....	....	2	1
No Treatment																		
106	M, 6	III	F	..	.....	.....	.....	..	.....	..	..	..	..	.....	.....	....	17	.....
Hodgkin's and Miliary Tuberculosis																		
35	M, 46	II	P	9	$\underline{0}$	$\underline{0}$	0	..	.....	..	..	..	..	0	.....	0	14	5

[1] Extent of disease: I = one group of nodes only; II = more than one group of nodes; III = lymph nodes and liver or spleen; IV = one viscus only, for example, stomach, and V = visceral and lymph nodes.

[2] Condition at time of initial therapy: G = minor symptoms or none, with or without evidence of disease; F = symptoms that prevent normal activity, and P = symptoms that produce invalidism or semi-invalidism.

[3] Remission includes period during which condition is G. Symbols are as follows:

6 = months remission from x-ray
6 = months remission from HN_2
$\overline{6}$T = months remission from TEM
6 + = still in remission
6* = remission after surgery only
6** = remission after both x-ray and HN_2 combined
0 = no remission from x-ray
$\underline{0}$ = no remission from HN_2

before the disease reached a refractory stage. While the same general principles of therapy were maintained throughout, no two patients were treated exactly alike. The cases are too few for further statistical breakdown as to amount of therapy, size of the fractions of the total dose and the like. Some of the patients who were given treatment considered adequate by the standards of most therapists did well, others did poorly. Some who received treatment considered inadequate by many did poorly, others did well. In a few patients foci of disease which were not treated regressed as other regions were tested. In other patients no change in the untreated disease was noted but the patient remained in remission after treatment of the major areas of disease only. In those receiving HN_2 after many successful courses of radiation, responses to HN_2 were brief.

Lymphosarcoma. Sixteen patients were treated by roentgenotherapy only, and an additional eight received roentgenotherapy initially with HN_2 given later in the course of the disease. The wide range of total remission and survival in this group of twenty-four patients is noted in Table III. Twenty-two patients were dead at the end of the study and the remaining two have died of lymphosarcoma since that time. As with Hodgkin's disease some patients had a long remission from a single course of treatment, others had responses of decreasing duration, and 20 per cent did not have a response of sufficient degree to be considered a remission.

Other Lymphomas. Data from the present series are insufficient for evaluation of the treatment of reticulum cell sarcoma and giant follicle lymphoma.

NITROGEN MUSTARD

Hodgkin's Disease. Seventeen patients received HN_2 after several courses of roentgenotherapy which were for the most part successful. While the HN_2 contributed to prolongation of remission in several patients, the responses usually were poorer than with previous roentgenotherapy. (Table II.)

Six patients received HN_2 therapy only, and in seven others this was the initial and principal therapy administered although roentgenotherapy was given later in the course of the disease. (Table II.) These patients had generalized disease. No patient with local or asymptomatic disease received HN_2 as the sole or initial therapy. Of the thirteen patients, ten survived the first year, five the second year, three the third year and one the fifth year. Two did not have a response of sufficient degree to be classified as remission. Two had single remissions of over four and six years, respectively, and the condition is still in remission. Both had had only one course of therapy. The good results were probably a consequence of the relatively benign nature of the disease in these two patients. The others had several courses, and individual remissions were short. As with roentgenotherapy, a tendency existed for the individual responses to get progressively shorter, but there were exceptions.

When HN_2 was the initial and principal therapeutic agent the results were similar to those obtained with the patients treated with roentgen ray. In some, long remissions occurred from a single course, in some remissions of varying duration with several courses occurred and some did not respond at all. The year by year survival rate was similar up to three years. After that it was poorer with the HN_2-treated group. It should be noted that all of the patients treated with HN_2 had generalized disease at the time of first treatment. In general, the survival time of the patients treated with HN_2 was less than that reported in the roentgenotherapy series in the literature. The latter include Hodgkin's disease in all stages. If one compares the present series of generalized cases of Hodgkin's disease treated with HN_2 (average survival twenty-four months, 8 per cent survived five years) with Peters'* group III or generalized cases treated with roentgenotherapy (average survival twenty-three months, 9 per cent survived five years), the results are very similar.

The value of HN_2 would be increased if it could be demonstrated that the agent was effective in cases that had become resistant to roentgenotherapy. In the present series none of five patients known to be resistant to roentgenotherapy had any significant response to HN_2. Of four known to be responsive to roentgenotherapy, all responded to HN_2. Of ten who had previously received roentgenotherapy but whose responsiveness had been unevaluated at the time of HN_2 therapy, seven had had some response to HN_2.

Lymphosarcoma. Six patients were treated with HN_2 only, and in three additional cases HN_2 was the initial therapy with roentgenotherapy given later in the course of the disease.

* PETERS, M. V. A study of survivals in Hodgkin's disease treated radiologically. *Am. J. Roentgenol.*, 63: 299, 1950.

TABLE III[1]

LYMPHOSARCOMA

Patient No.	Sex and Age	Extent of Disease	Condition	Duration Prior to Therapy (mo.)	Months Remission Each Course of Therapy									Duration of Remission (mo.)			Survival Time (mo.)	
					1	2	3	4	5	6	7	8	9	Total	From X-ray	From NH_2	Total	After Therapy
Roentgenotherapy Only																		
104	F, 44	III	F	1	46	3	15	38	8	13	7	18	2	.....	.....	....	.....	.....
					4	2	0	....	.....	....	....	..	..	.....	156	....	161+	160+
47	F, 48	III	G	3	60	3	18	1+	.....	....	....	..	..	.....	82+	....	85+	82+
135	M, 76	V	G	2	64	....	....	....	.....	....	....	..	..	.....	64	....	68	66
66	F, 48	II	F	..	48	....	....	....	.....	....	....	..	..	.....	48 ..	....	.....	51
127	M, 73	II	G	1	3	8	....	....	.....	....	....	..	..	.....	11	....	18	17
134	F, 49	I	G	15	10	....	....	....	.....	....	....	..	..	.....	10	....	33	18
63	M, 60	II	..	6	6	....	....	....	.....	....	....	..	..	.....	6	....	13	7
140	M, 69	III	F	14	5	0	....	....	.....	....	....	..	..	.....	5	....	20	6
132	F, 76	IV	G	3	4	....	....	....	.....	....	....	..	..	.....	4	....	12	9
45	F, 76	II	F	4	4	0	....	....	.....	....	....	..	..	.....	4	....	12	8
136	M, 60	V	F	1	2	....	....	....	.....	....	....	..	..	.....	2	....	6	5
129	M, 11	II	G	1	1	1	....	....	.....	....	....	..	..	.....	2	....	5	4
125	M, 70	III	G	2	0	....	....	....	.....	....	....	..	..	.....	0	....	12	10
48	F, 60	V	P	3	0	....	....	....	.....	....	....	..	..	.....	0	....	12	9
124	M, 55	V	F	5	0	0	....	....	.....	....	....	..	..	.....	0	....	6	1
137	F, 65	V	F	1	0	....	....	....	.....	....	....	..	..	.....	0	....	2	1
Roentgenotherapy Initially—HN_2 Later																		
46	M, 73	II	F	26	18	12	18	14	10	0	0T	..	..	72	18	54	106	80
49	F, 49	II	G	19	2*	12	2	13	5	3	0	..	..	39	32	3	65	46
43	F, 50	III	..	6	24	3	0	....	.....	....	....	..	..	27	27	0	36	30
64	M, 54	II	G	3	5	3	6	2	5	0	....	..	..	21	10	11	26	23
80	M, 50	II	G	..	14**	3	0**	....	.....	....	....	..	..	17	10	7	.....	22
61	M, 46	II	G	9	9	0	0	0	.....	....	....	..	..	9	9	0	27	18
56	F, 78	II	..	3	3	4*	0	....	.....	....	....	..	..	7	3	0	14	11
51	M, 17	V	G	8	0	0	....	....	.....	....	....	..	..	0	0	0	10	2
HN_2 Therapy Only																		
57	M, 29	II	P	1	14	66+	....	....	.....	....	....	..	..	.....	.....	80+	81+	80+
42	F, 78	II	G	17	5	6	5	8	5	6	5	7	6T	.....	.....	....	.....	.....
					5T	2T+	....	....	.....	....	....	..	..	.....	.....	61+	78+	61+
44	M, 53	V	F	2	8	8	....	....	.....	....	....	..	..	.....	.....	16	18	16
60	F, 53	III	G	19	8	6	....	....	.....	....	....	..	..	.....	.....	14	34	15
67	F, 66	II	G	47	3	3	0	0	0	0	....	..	..	.....	.....	6	83	36
50	F, 56	V	P	7	0	....	....	....	.....	....	....	..	..	.....	.....	0	7	0
HN_2 Initially—Roentgenotherapy Later																		
79	M, 42	II	G	24	3	16	4	4**	6	8+	....	..	..	41+	16+	25	65+	41+
55	M, 52	III	G	13	10	9	3	5	.....	....	....	..	..	27	17	10	48	35
59	M, 47	III	P	3	0**	....	....	....	.....	....	....	..	..	0	0	0	5	2
Surgery Only																		
128	F, 65	IV	F	1	....	....	....	....	.....	....	....	..	..	0	.....	....	1	0
No Treatment																		
58	F, 47	III	F	..	....	....	....	....	.....	....	....	..	..	.....	.....	....	15	.....
131	M, 52	V	P	..	....	....	....	....	.....	....	....	..	..	.....	.....	....	10	.....
133	M, 63	II	G	..	....	....	....	....	.....	....	....	..	..	.....	.....	....	8	.....
73	F, 67	V	F	..	....	....	....	....	.....	....	....	..	..	.....	.....	....	7	.....
146	M, 60	III	P	..	....	....	....	....	.....	....	....	..	..	.....	.....	....	4	.....
Giant Follicle Lymphoma																		
72	F, 70	I	G	1	12	9	6	17	8	4	8	..	..	64	64	....	69	68
69	M, 31	II	G	13	7	5	4	6T	14T+	....	....	..	..	36+	4	32+	49+	36+
145	F, 59	I	G	1	7	11	4	8	.....	....	....	..	..	30	18	12	39	38
143	M, 64	III	F	7	12	....	....	....	.....	....	....	..	..	12	12	....	27	20
68	F, 38	III	G	6	5	1	....	....	.....	....	....	..	..	6	.....	6	18	12
71	F, 74	I	G	4	3	0	....	....	.....	....	....	..	..	3	3	....	12	8
70	F, 63	III	P	12	0	0	....	....	.....	....	....	..	..	0	.....	0	14	2
Reticulum Cell Sarcoma																		
81	F, 52	I	G	1	48+	....	....	....	.....	....	....	..	..	48+	.....	48+	49+	48+
126	M, 68	V	G	6	2	....	....	....	.....	....	....	..	..	2	2	....	10	4
74	M, 59	III	G	13	0	....	....	....	.....	....	....	..	..	0	0	....	14	1
141	M, 77	V	G	1	No therapy	....	....	....	.....	....	....	..	..	.....	.....	....	3	.....

[1] See Table II for explanation of symbols.

(Table III.) Total remissions varied from 0 to 80 months, and remission from a single course of therapy persisted up to sixty-six months. Two patients did not show a distinct remission. As a group the HN_2-treated patients showed longer remissions than the patients receiving roentgenotherapy but this group is too small for valid comparison. Four patients were known to be resistant to roentgenotherapy and none responded to HN_2. One patient known to be resistant to HN_2 did not respond to roentgenotherapy. One patient known to be sensitive to roentgenotherapy responded to HN_2. As with Hodgkin's disease, no real remission could be produced by HN_2 in cases known to be resistant to roentgenotherapy.

DISCUSSION

A comparison of our data with those of others is included in part II of this report. From the material presented, several conclusions can be drawn.

When nitrogen mustard is used as the sole therapy for a patient with malignant lymphoma the course of the disease is very similar to that when roentgenotherapy is used. As with the patient receiving roentgen ray treatment, the progress of the disease varies widely from patient to patient. If a patient has been demonstrated to be resistant to one form of therapy, no significant response to other forms of treatment will occur. If a patient has been known to be responsive to one agent, he will respond to the other.

If one agent is used during the early part of the disease and a second agent used later, the first used will usually be more effective, whether it is roentgenotherapy or HN_2. It appears that both agents are similar in mode of action and effectiveness. It should be noted that this report measures only effectiveness in producing remission. No data are presented to compare the effectiveness of HN_2 with roentgenotherapy in reducing tumor masses, in the duration of response from single courses of treatment, in the speed of action or in toxicity. All of these factors are very important and will be discussed in part II of this report.

Has HN_2, when used in the manner of the present report, resulted in any increase in the total period of remission beyond that which could be obtained by roentgenotherapy? This has been evaluated by comparing total remissions during the period 1940 to 1946 when only roentgenotherapy was available with those of the period 1947 to 1953 when both were used. These data (Table IV) were taken from a table of data on remission, based on the principle of a standard life table with end of remission used in place of end of life. All lymphomas are grouped together, which is permissible for this purpose since the ratio of the several types was about the same year after year. The data indicate that from 1947 to 1950 there were more patients who had short remissions of six months to one year than before HN_2 was available but there were fewer with remissions over two years. The figures for two years and over for the 1947 to 1950 period may be somewhat misleading because of the shorter follow-up period for this group. Certainly the data do not suggest any striking improvement in the overall results of the treatment of lymphomas by the addition of HN_2. A slight increase in the number of short remissions may have occurred which suggests that patients in whom the disease responded only slightly to roentgenotherapy reveal slightly longer remissions now that HN_2 has been added.

TABLE IV

ALL CASES OF TREATED LYMPHOMA GROUPED AS TO PERIODS 1940 TO 1946 AND 1947 TO 1950

	Years						
	0	½	1	2	3	4	5
1940 to 1946 Group:							
Number in remission at anniversay	66	38	31	26	24	20	16
Number ending remission	..	28	7	5	2	4	4
Per cent in remission	..	58	47	39	36	30	24
1947 to 1950 Group:							
Number in remission at anniversary	42	30	21	11	9	5	2
Number ending remission	..	12	9	10	2	1	1
Last observed still in remission	..	..	..	..	3	2	1
Per cent in remission	..	71	50	25	21	13	..

SUMMARY

Results of therapy in 116 cases of malignant lymphoma are presented. Little difference could be demonstrated in the effectiveness of nitrogen mustard, used as the sole or principal therapy, when compared with the effectiveness of roentgenotherapy in producing and maintaining remissions.

Therapy of the Malignant Lymphomas*

II. A Review

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WHEN we began to compile and analyze the data presented in part I of this study, the difficulties in drawing reliable conclusions from a study of the therapy of malignant lymphomas became obvious. A careful and critical review of the data of others revealed that they also encountered similar problems. In respect to the effect of specific types of therapy, technics of therapy, the effect of therapy on the length of life and other aspects of therapy, conclusions have been drawn without sufficient evidence. In some instances the investigators concluded more than their data would permit; in other instances reviewers have concluded more from a report than the original investigators intended.

The purpose of this review is twofold. With the many new treatments for lymphoma beginning to appear, it seemed appropriate to try to determine which of the current opinions of present day therapy have been proven and which have not been substantiated.

Almost all of the information contained in this report is derived from studies in the literature which we considered significant because of number of cases, adequate follow-up, adequate presentation of data and histologic confirmation of diagnosis. For the most part data have been taken from the original source, and the use of data from review articles has been avoided. In some instances the data are presented differently than in the original report; in those situations they have been recalculated so as to make them comparable.

SURGERY

Hellwig[1] and Gall[2] advocated surgical treatment of lymphomas. In interpreting any result of such therapy it must be kept in mind that all patients so treated have what is believed to be local disease and cannot be compared with any group that includes all clinical stages of lymphomas.

Hodgkin's Disease. Hellwig reported a five year survival of 15 per cent and Gall a five year survival of 45 per cent after surgical treatment. Many of Gall's patients were also treated with roentgenotherapy. In a comparable group treated by roentgenotherapy alone and reported by Lenz, Wells and Stout,[3] 27 per cent survived five years. In Peters'[4] group I of patients with localized disease 88 per cent survived five years and 77 per cent survived ten years after treatment with roentgenotherapy only. Except for scattered cases, few data appear in the literature regarding the surgical treatment of Hodgkin's disease. The data do not indicate any superiority of this form of treatment since comparable cases treated with roentgenotherapy alone have as long a survival.

Other Lymphomas. Gall[2] and Hellwig[1] reported good results from surgical treatment of lymphosarcoma and reticulum cell sarcoma. In many cases roentgenotherapy was used in addition. In the series of 119 cases of the lymphosarcoma group reported by Stout,[5] fifteen patients who were free of disease at five years were free of disease at ten years, suggesting that these patients were cured. These good results were obtained either by surgical removal or by roentgenotherapy, and there was no indication that one type of therapy was preferable to the other. Sugarbaker and Craver[6] also believed that good results could be obtained by either approach. Shimkin et al.[7] presented cases of lymphosarcoma treated by either method which he assumed to be cured. No data are available that evaluates combined therapy as compared to either surgery or roentgenotherapy used alone.

In the aforementioned series the primary

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disease was in the viscera in a large number of cases considered cured. In Hellwig's series only a third of the 130 patients had an extra-lymphatic primary focus, but of the twenty-six patients free of disease thirteen were of this group. Of Stout's patients treated for lymphosarcoma, the lymph nodes were involved in eighty-three; only six of these patients were free of disease ten years later. Of thirty-five subjects with disease of the viscera nine were free of disease ten years later. Forty-four of the 215 cases of lymphosarcoma reported by Shimkin et al. had involvement of areas other than lymph nodes, such as stomach, bone, and the like; but eight of ten of the patients considered cured were of this group. It appears that in patients with localized disease, especially if the primary site is a viscus and not a lymph node, eradication either by surgery or roentgenotherapy is indicated. Perhaps technical factors would make one form of treatment preferable to the other in particular situations, but this has not been evaluated. When lymphosarcoma is localized to the stomach or another internal viscus, exploration is needed for diagnosis and radical removal is then the logical course.

Since patients with Hodgkin's disease apparently may be free of disease for periods up to twenty-five years after a biopsy with or without subsequent roentgenotherapy and then have recurrences,[8–10] caution is necessary in classifying long survivals as cures after radical surgery. Patients with lymphosarcoma are less likely to have long, asymptomatic remissions followed by relapse. Consequently a five to ten year remission without evidence of disease is more likely to represent eradication of the disease in a patient with lymphosarcoma than in one with Hodgkin's disease. We agree with Stout[11] that with our present knowledge we can think in terms of cure when dealing with localized lymphosarcoma but not when dealing with Hodgkin's disease.

ROENTGENOTHERAPY

Many studies have been reported on roentgenotherapy of lymphomas but there are still many unanswered problems regarding the influence of therapy on the course of the disease and regarding preferred therapeutic technics. The only approach to these problems is through comparison of the results obtained by different therapeutic methods. Such a comparison requires a comparable series, and very few of the many series in the literature were comparable. Some of the variables appeared frequently in the several reports on the therapy of lymphomas. The portion of the population with a particular lymphoma which was seen at each institution varied widely. In some hospitals many patients in the early stages were seen while in others the patients were predominantly in the late stages. The proportion varied as to age, sex, race, and the like. Histologic criteria for diagnosis were not uniform. Some reports excluded patients too ill for therapy while others did not. Several studies included not only those cases first diagnosed and treated during the period of study but included in addition survivors from previous periods who were retreated during the period of study. Inclusion of survivors of previous periods and exclusion of those who died obviously weights a series with the more favorable cases. Some studies were handicapped by a large group of patients lost to follow-up. In some cases this group was made up of patients who were lost because the condition was still in remission and the patients had not returned to their physician. In other cases the group consisted primarily of those patients who had died and could not be traced. Some investigators evaluated a particular technic of therapy, yet that therapy was not used during the entire period from which their data were compiled. Some studies included both patients who were living and those who were dead while others included only the dead.

Because of this variability between series, only rough comparisons are valid. Different types of therapy are best evaluated by the same institution, using the same standards throughout. There have been few such comparative studies.

Hodgkin's Disease. In Table 1 data are presented from different series representing varying uses of roentgenotherapy. To evaluate therapy in a disease, it is necessary to know how the disease behaves without therapy. The only large series of untreated cases reported is a group of 163 patients, part of the series of Minot and Isaacs.[12] None of the patients in the entire series of 238 cases or that of Desjardins and Ford[13] received the high voltage, systematic roentgenotherapy that is now used. Minot and Isaacs combined all lymphomas in the series. The data were based only on those patients who died, and duration of life was calculated from estimated onset of disease. Almost all of the other studies measured survival from diagnosis. These studies were made before the days of antibiotics and liberal blood trans-

TABLE I

HODGKIN'S DISEASE

Series	Period	Cases	Died	Survival (%)					Average Survival (yr.)	
				1 yr.	2 yr.	3 yr.	5 yr.	10 yr.	Since Therapy	Since Onset
1. No Roentgenotherapy										
**Minot, Isaacs (1926)	1913 to 1925	163	163 (All lymphomas included)	*67	*41	*25	*12	*2	.....	*2.5
2. Minimal Roentgenotherapy										
**Desjardins, Ford (1923)	1915 to 1919	92	82	*88	*62	*36	L 90 *9.6	L 33	.....	*2.6
**Minot, Isaacs (1926)	1913 to 1925	238	238 (All lymphomas included)	*84	*48	*29	*19	*1	.....	*2.9
3. 180–250 Kv. Local Therapy. Total Local Dose 400–2,500 r. Manifest Lesions Only										
Gilbert (1937)	1922 to 1937	52	36 (21 with incomplete therapy excluded)	#83	#66	#56	#40	.....	*2.6	*3.9
Slaughter, Craver (1942)	1918 to 1935	265	239	#68	#49	#36	#18	#2.3	*2.1 #2.8	....
Merner, Stenstrom (1947)	1926 to 1942	185	160	#60	#46	#36	#22	#11	#2.8	#4.1
Gellhorn, Collins (1951)	Not stated	65	46	#78	#67	#61	#40	.....	.....	....
Present cases (x-ray)	1940 to 1950	48	44	#62	#39	#35	#18	#2.1	#2.6	#3.3
4. Local Treatment as in Section 3 Plus Prophylaxis										
Higley, Hauser (1939)	Not stated	68	67	#44	#21	#15	#4	#1.5	.....	....
5. 200–400 Kv. Total Local Dose to Lesions 1,800–5,000 plus Prophylaxis										
Peters (1950)	1924 to 1942	113	75	#78	#62	#60	#53	#31	#7.0	#8.5
6. Local Treatment as in Section 3 plus Total Body Radiation										
Medinger, Craver (1942)	Not stated	94	75	#80	#65	#50	#24	.....	#3.5	*3.7
7. Radium Pack										
Burnam (1926)	1913 to 1925	173	110 (26) (lost)	*85	*62	*43	L 41 *15	L 11	*2.8	*4.3
8. Local Treatment as in Section 3 plus Nitrogen Mustard										
Gellhorn, Collins (1951)	Not stated	67	34	#75	#68	#51	#38	.....	.....	....
9. All Types of Therapy										
Present (1954)	1940 to 1950	64	55	#64	#40	#32	#20	.....	#2.7	#3.5

* = Based on dead patients only.
L = Based on living patients only.
# = Based on living and dead.
** = Survival calculating from onset of disease.

fusions. Minot and Isaacs concluded that the apparent longer survival of those patients receiving roentgenotherapy was due to the greater number of more favorable cases in that group.

From about 1925 to the present day the most widely used therapy has been high voltage (200 to 250 kv) radiation given to the obvious lesions in fractional doses to a total of 500 to 2,500 roentgens in air per area of disease. Retreatment is given to recurrences. Table 1 gives the data from several series in which roentgenotherapy was employed. The results of some of these studies suggest improvement in survival especially if the three and five year survival rates are used as measures. With so many variables to be considered, it is impossible to be certain that this type of roentgenotherapy has resulted in an increase in survival. In speaking of survival we are considering group survival; increased survival of a small number of patients might not be reflected in the statistics of the group. Occasionally patients are in danger from masses obstructing the trachea, spinal canal, intestine or common bile duct and their life is prolonged by therapy which relieves the obstruction.

Some radiologists treat the various foci and, in addition, give smaller amounts to lymph nodes which may or may not be involved. Higley and Hauser[14] used this approach and, as indicated in Table 1, their results were poor. They were in fact, worse than has often been reported for untreated cases. The reason for this is not clear. Hynes and Frelick[15] used a similar approach but the number of cases so treated was small.

Medinger and Craver[16] used conventional therapy to local disease and in addition gave total body radiation. This series is best compared with another series from the same institution, that of Slaughter and Craver[10] using conventional therapy only. Comparison (Table 1) indicates a slight improvement in survival with the addition of total body radiation, at least for the first three years of follow-up. A symptomatic response to total body radiation above that obtained by local therapy was noted.

The studies cited were based on local treatment to a point beyond that needed for regression of the disease. The amount of radiation given was less than could be tolerated and less than is often given in attempting to eradicate tumors of other types. Recurrences were retreated. Some radiotherapists believe that a better result can be obtained by giving higher doses to local disease in the hope that local recurrences can be prevented, and the course of the disease slowed. In evaluating this approach it should be kept in mind that the goal in therapy is not only the effect on local foci but on the disease as a whole. Lenz, Wells and Stout[3] advocated this approach but unfortunately did not give sufficient data for comparison with other studies. Peters[4] also used higher local doses and, in addition, over half of these patients received smaller amounts of radiation to areas not clinically involved. Her results were better than those in any other series. Comparing the group receiving prophylactic therapy with the group receiving local therapy only, no improvement was noted in the five year survival rate of the patients with local disease but there was a 14 to 17 per cent improvement in the groups with more extensive disease. While the figures presented in Table 1 are concerned with the entire group with Hodgkin's disease, Peters classified her results as to groups of patients in a particular stage of the disease. This is a desirable approach but for comparison with other studies all her cases were combined into a single group. It must be noted that Peters' series contained a higher percentage of patients with localized disease (31 per cent) than the series of Medinger and Craver (14 per cent) and the percentage (18 per cent) in the series reported in part 1 of the present study. Of Peters' original 257 cases, 144 were eliminated. In 60 of these cases there was no biopsy, and in 84 cases a review of the microscopic slides did not confirm the diagnosis or the slides could not be reviewed. If the part of the 144 patients who had Hodgkin's disease but were eliminated from analysis had more advanced disease than the 113 upon whom conclusions were based, the results would not be as favorable as reported. The differences between the results of Peters' study and the studies of investigators who did not use roentgenotherapy or used minimal doses are so great that they are probably significant. The differences between Peters' results and those of Gilbert and of Gellhorn and Collins (Table 1) could be accounted for by the many variables common to all studies of lymphoma and do not necessarily indicate the superiority of her therapy. If Peters' better results were due to better technics of therapy and not to the type of patients treated, future reports from other institutions should support her findings.

Lymphosarcoma. Virtually all the difficulties outlined in comparing the various experiences in therapy of Hodgkin's disease pertain equally to the study of the therapy of lymphosarcoma. In addition, relatively few studies of the treatment of lymphosarcoma are available, and there is no uniformity in what is classified as lymphosarcoma.

Stout[5] indicated that long survival and probable cures resulted from eradication of localized disease. Comparison of the series of Lenz, Wells and Stout,[3] Leucutia,[18] and Nathanson and Welch[19] with that of Desjardins and Ford,[13] who used low voltage x-ray therapy in an unsystematic manner, suggests an improved five year survival rate with the use of modern technics. (Table II.) The evidence is not conclusive. A large number of patients who died before five years had symptomatic relief and a reduction of tumors from roentgenotherapy but there was insufficient evidence to determine if life was prolonged. Leucutia did show data suggesting that life was prolonged.

It is impossible to conclude from the literature what technics of roentgenotherapy are best. The basic therapy in most reports was radiation from a 200 to 250 kv source. Usually 1,000 to 5,000 r in air were administered to a focal area of disease. In addition, some therapists such as Leucutia treated clinically uninvolved lymph nodes. The results were good but no better than those of Lenz et al. who gave only local therapy. Hynes and Frelick[15] also administered prophylactic roentgenotherapy but the total number of cases was small.

Medinger and Craver[16] added total body radiation to local therapy in thirty patients with generalized disease. They believed that more symptomatic improvement resulted than with conventional therapy and that the duration of remission was longer. Since the series was small and no control series of similar clinical types was provided for comparison, it is difficult to draw definite conclusions.

Lenz et al.[3] advocated the use of large dosages of roentgenotherapy to foci of disease in an effort to prevent recurrences in that area. From evidence gained by determining recurrence rate over a two year period after various doses, they advised tumor doses of 4,000 to 5,000 r when the disease was local and when other conditions did not prohibit this procedure. The data cited by them are insufficient to indicate whether this approach increased the total period of remission above that obtained by smaller doses with retreatment of recurrences. The frequency of local recurrence was significantly decreased.

NITROGEN MUSTARD

Hodgkin's Disease. Many reports are available on the use of methyl bis (beta chloroethyl) amine hydrochloride (HN_2) in the treatment of lymphomas. For the most part, follow-up has been brief and experience has been limited to cases with generalized disease. Consequently there is a great deal of information on the effect of HN_2 on specific manifestations of Hodgkin's disease but little on the total course of the disease. The data presented in part I of this report suggest that HN_2 therapy does not differ significantly from roentgenotherapy in this regard. It has not been determined that either type of therapy prolongs life.

It is important to evaluate the effect of HN_2 on disease that has become resistant to roentgenotherapy. Our data indicated that when resistance to roentgenotherapy occurred, a remission from HN_2 was unlikely, although there might be a brief or incomplete response.

These findings are similar to those of Alpert et al.[20] Spurr et al.[21] observed equal survival periods following HN_2 in the radio-sensitive and radio-resistant groups. Measurement of survival only is no indication of different symptomatic responses between the two groups. Dameshek et al.[22] observed good remission in two patients in whom response to roentgenotherapy had been poor.

Those who used HN_2 as an initial form of therapy and had some basis for comparison concluded that individual remissions from HN_2 were shorter than with roentgenotherapy.[20,21,23] None of these studies included an evaluation of roentgenotherapy for comparison but the remissions from HN_2 were brief. Ap Thomas and Collumbine[24] included twenty cases with generalized disease treated with roentgenotherapy and found an average remission of nine and a half months following one course of therapy as compared with an average of two months in a similar group treated with HN_2. One patient in the present study (part I) has lived fifty-two months and another seventy-five months without recurrence, illustrating that long remission does occur. As with other types of therapy, it was not clear whether the long remissions were due to treatment or to the benign nature of the disease.

TABLE II†

LYMPHOSARCOMA

Series	Period	Cases	Died	Survival (%)					Average Survival (yr.)	
				1 yr.	2 yr.	3 yr.	5 yr.	10 yr.	Since Therapy	Since Onset
1. Minimal and Non-systematic Roentgenotherapy										
**Desjardins, Ford (1923)	1915 to 1919	76	67	*63	*39	*31	L 78 *11	....	.....	*2.45
2. Surgery with and without Postoperative Roentgenotherapy (Localized Disease Only)										
Gall (1943)	.....	14	9	#72	#57	#50	#36	#7.2	.....	.....
3. Roentgenotherapy (Technic Not Stated)										
**Nathanson, Welch (1937)	.....	310	309	#79	#50	#36	#23	#1.6	.....	.....
4. High Voltage Local Therapy. Total Local Dose 1,000–5,000 r. Manifest Lesions Only										
Howes, Levin (1943)	1936 to 1940	47	34	...	...	...	...	.....	L 4.1 #1.6	.....
Lenz, Wells, Stout (1950)	1918 to 1940	242	197	...	...	...	#27	#17	.....	.....
Present (1954)	1940 to 1950	24	22	#42	#29	#25	#17	#4	#2.3	#2.8
5. Local Therapy as in Section 4 Plus Retreatment of Lesions Regardless of Status and Prophylaxis										
Leucutia (1934)	1922 to 1930	31	24	...	...	...	#30	#15	*2.1	*3.3
6. Local Therapy as in Section 4 Plus Total Body Radiation (General Disease Only)										
Medinger, Craver (1942)	.....	30	27	#60	#40	#38	#11	0	#2.0	#3.2
7. All Types of Therapy										
**Shimkin et al. (1954)	1913 to 1948	215	195	#71	#50	#39	#24	#6	.....	.....
Present (1954)	1940 to 1950	34	29	#53	#36	#30	#21	#3	#2.3	#3.0

* = Based on dead patients only.
L = Based on living patients only.
\# = Based on living and dead.
** = Survival calculated from onset of disease.

† The following types of lymphoma are included in each series: Lenz, Wells and Stout—lymphocytic, reticulum cell and follicle lymphoma; Leucutia—lymphocytic, reticulum cell and follicle lymphoma; Nathanson and Welch—lymphocytic, reticulum cell and follicle lymphoma; Shimkin et al.—lymphocytic, reticulum cell and follicle lymphoma; Howes and Levin—lymphocytic and reticulum cell lymphoma; Medinger and Craver—lymphocytic and reticulum cell lymphoma; Gall—lymphocytic; Present—lymphocytic; and Desjardins and Ford—not stated.

The reduction of tumors varied greatly from case to case.[20] All patients showed some response in lymph node and visceral lesions, and in some complete regression occurred. Those who have reported the effect on masses which had been uninfluenced by previous therapy believed that HN_2 was not as effective in the reduction of tumors as roentgenotherapy.[20,21,58] Alpert et al. reported several cases of patients who did not have complete regression of nodes following one or more courses of HN_2 therapy but who did have complete and prolonged regression with subsequent roentgenotherapy. In some cases they correlated poor response to HN_2 with large amounts of fibrosis in the nodes or with poor blood supply. Spurr et al. believed that node responsiveness was related to the age of the disease.

Spurr et al. stated that HN_2 should be used when there are pressure symptoms resulting from a mass of lymphomatous tissue. Holmes and Shulz[25] and Lenz, Wells and Stout[3] stated that symptoms of obstruction of mediastinal structures by involved nodes may increase immediately after roentgenotherapy. A brief search of the literature failed to reveal cases supporting the opinions that roentgen radiation will increase obstruction of mediastinal structures due to lymphoma, or that there is an increase in the size of a mass of lymphomatous tissue prior to reduction in size. Many instances of treatment of mediastinal lymphoma by radiation without aggravation of obstructive symptoms have been noted. The radiologist in one of our institutions has personal knowledge of an occurrence of almost complete tracheal obstruction following the start of roentgenotherapy in one patient. No instances of aggravation of pressure symptoms by HN_2 have been reported. Available evidence indicates that HN_2 is preferable when mediastinal obstruction is present. Treatment of obstructing spinal canal lesions is a similar problem but has not been studied.

Nitrogen mustard treatment usually gives relief of such symptoms as fever, malaise, pruritus and abdominal pain in a variety of clinical types of Hodgkin's disease.[20–24,26] Spurr et al.[21] and Wintrobe and Huguley[23] found a prompt reduction in fever in those whose response in general was good. Alpert et al.[20] reported good results with the "occult febrile" type of disease.

Gellhorn and Collins[27] treated sixty-three patients with generalized disease of varying extent with a combination of roentgenotherapy and HN_2. (Table 1.) These patients were compared with sixty-five patients, including all types of Hodgkin's disease, treated with roentgenotherapy alone. The groups were not equal in composition since the latter included cases with local disease. No difference in survival occurred but radiation time was reduced by one half in those patients receiving HN_2. As already noted, slight improvement of results has been obtained by adding total body radiation or prophylactic roentgenotherapy to standard local therapy. Perhaps this can be accomplished more easily and rapidly by the use of HN_2 in addition to local roentgenotherapy.

Previous reports[20,22,23] have dealt extensively with the effects of HN_2 on the hematopoietic and gastrointestinal systems and very little regarding these will be added in this report. In none of the series was this a major problem. Alpert et al. used up to eleven courses of therapy in one year and reported no serious difficulties. Wintrobe and Huguley used HN_2 when one or more of the blood cellular elements was depressed and reported no deaths from drug toxicity. Leukopenia was diminished in some patients following HN_2 therapy. In Hodgkin's disease cytopenias from secondary hypersplenism, hemolytic anemia, marrow invasion and from unknown causes may occur. The optimum type of therapy to use in these various situations is unknown at the present time. Spitz[28] reported a cumulative effect on the marrow, but her data are insufficient to support a final opinion. It is evident that Hodgkin's disease reaches a stage when the tumor is much less responsive than the bone marrow. In such instances there would be no point in giving HN_2 to improve hematopoiesis. In the series reported in part 1 no patient found unresponsive to a course of HN_2 (or to roentgenotherapy) responded to additional courses of HN_2. Probably persistent treatment of patients in whom the response has been minimal with roentgenotherapy, HN_2 or triethylene melamine (TEM) does more harm than good.

Gellhorn and Collins[27] reported a case of miliary tuberculosis developing after HN_2 therapy. Meyer[49] reported a similar case after administration of TEM and cortisone and a second case after TEM alone. The symptoms and signs of miliary tuberculosis may be so similar to those of lymphoma that all of these patients could have had both diseases prior to

HN_2 or TEM. One of the patients in the present series reported in part I died with miliary tuberculosis after three courses of HN_2 therapy. However, a comparison of clinical and autopsy findings indicated that both diseases existed prior to treatment. A similar situation existed with the case reported by Kurnick et al.[29] It is interesting that our patient had symptomatic improvement after two of the courses of HN_2 although the symptoms were probably due to tuberculosis. In the past year we have seen three additional patients with a combination of tuberculosis and lymphoma. One developed disseminated tuberculosis in the cervical nodes two years after treatment of the combined diseases with roentgenotherapy and with streptomycin. This patient had never received HN_2 or TEM. Two patients had active pulmonary tuberculosis at the time of HN_2 therapy. One was receiving streptomycin at the time of HN_2 therapy and the other several weeks later. In neither case was there an increase in pulmonary disease or dissemination of the tuberculosis. Both patients died of lymphoma and the postmortem examination revealed localization and good control of the tuberculosis.

Five cases have been reported of patients who had a combination of lymphoma and cryptococcosis and have received HN_2 therapy.[30–32] In three of these signs of central nervous system cryptococcosis first appeared a month after the HN_2 treatment. In the remaining two the cryptococcosis remained localized. The problem of the effect of HN_2 on the resistance to tuberculosis and other infections requires further study.

Lymphosarcoma. In the study reported in part I, lymphosarcoma responded in a manner similar to that observed with Hodgkin's disease. When HN_2 was used as an initial form of therapy, a wide variation in results was achieved as was found when roentgenotherapy was used initially. None of the patients had localized disease. Others have noted varied responses to HN_2 in patients who have received previous roentgenotherapy.[20,21,23,29] Of the cases reported in the literature very few patients had HN_2 as the sole or initial therapy. However, Spurr et al. presented five such cases, four of which had remissions of twelve to fifty-three months and three of which were still living. One was alive and well fifty-three months after a single course of HN_2. No reports have been made of the use of HN_2 in disease with a single focus. Since there is a possibility that localized lymphosarcoma may be cured by other therapy, HN_2 alone should not be used.

TRIETHYLENE MELAMINE (TEM)

Several reports have been made on the treatment of the lymphomas with TEM.[33–41] In all studies the patients either had extensive disease or were no longer responding to other treatment. Follow-up periods were brief. No evidence exists to suggest that there is any basic difference between the actions of TEM and HN_2. TEM can be given orally and has been useful in situations where this factor was desirable. Almost all patients receiving HN_2 have gastrointestinal side effects. Only about 50 per cent of patients receiving TEM experienced anorexia, nausea or vomiting, and these symptoms were mild and less severe than following HN_2 therapy. With the types of cases of lymphoma treated so far, TEM reduced tumors, although often incompletely, and relieved symptoms to varying degrees. It cannot be stated whether TEM is more or less effective than HN_2 in relieving symptoms but it appears that the response is somewhat slower. Remissions have tended to be short. The effect of TEM on survival has not been determined.

Almost all of the patients treated have had Hodgkin's disease. The experience with other lymphomas has not demonstrated any basic difference in response.

Bone marrow depression was the major toxic effect of TEM. Usually this depression was transient but severe depression was more common with TEM[33] than with HN_2. It was often slower developing than with HN_2 and was more prolonged. Oral TEM was less predictable than HN_2 and the margin of safety appeared less. Patients with chronic lymphatic leukemia and lymphosarcoma were more sensitive than those with other lymphomas.[35]

ACTH AND CORTISONE

While there are reports of the use of ACTH and cortisone in the treatment of lymphomas, the total number of cases is small, and almost all the patients were in poor condition prior to therapy.[42–45] A few patients had a reduction in size of lymphomatous tumors and others experienced a loss of symptoms. Remissions were brief. Hormones have not consistently produced reduction of tumors comparable to roentgenotherapy or symptomatic improvement comparable to that obtained with HN_2 or TEM.

Rosenthal et al.[43] reported the beneficial use of hormones in the treatment of hemolytic anemia due to lymphoma. Straus et al.[45] observed an increase in cellularity of both normocellular and hypocellular bone marrows following cortisone therapy. Elements of the erythrocytic, granulocytic and megakaryocytic series were increased. These changes could not always be correlated with changes in the peripheral blood but the patients required fewer blood transfusions while receiving cortisone therapy.

OTHER DRUGS

The present discussion is confined to those agents that are now widely used in the therapy of lymphomas. Recently, triethylene phosphoramide (TEPA)[46,47] and triethylene thiophosphoramide (Thio-TEPA)[48] have been tried in the treatment of lymphomas. Their basic action is believed to be similar to that of TEM or HN_2.

PLANNING OF STUDIES OF THERAPY OF LYMPHOMAS

The knowledge gained from past studies of the therapy of lymphomas has been severely limited by the confusion of methods of study. Unless methods are standardized, future reports of old or new types of therapy will be equally inconclusive. The first step is to determine exactly what information is sought. One may wish to evaluate the effect of a therapeutic agent on survival, on constitutional symptoms, on the size of lymph nodes, on a specific manifestation such as hemolytic anemia, or the effect in cases known to be resistant to other therapy or of combining the unknown agent with one of known effect, and the like. The same principles do not apply to all of these types of study.

Selection of Clinical Material. The diagnosis in cases used for such studies should be proven by biopsy. Published records of the cases should include sex, estimated date of onset, age at time of diagnosis, date of diagnosis and the stage of disease at the time of treatment. Previous therapy is not a cause for exclusion of the patient in the majority of studies but the patient should be in relapse at the time of the study and there should be no possibility that the effect of the former therapy will be manifested while the new agent is being tested. For complete evaluation of an agent all stages of disease should be included, but if a new and potentially toxic agent is to be used the initial trial will almost inevitably be on late cases. It must be remembered that the standard of therapy, roentgenotherapy, does not have the same effect in late cases as it does at the time the disease is early and localized. New drugs may behave in the same manner, and any conclusions drawn from the use of a drug in late, therapy-resistant patients cannot be applied to the disease as a whole.

If a form of treatment shows great promise, it may be desirable to learn if it is suitable as the initial therapy in all stages of lymphoma, or if it will prolong life. In this type of study the patients should not have received previous therapy. No selection of cases should be made. The case material should include early and late cases in a normal proportion, if possible. In some situations selected cases might be used as, for example, would be necessary in studying the results of surgery in disease localized to one group of lymph nodes. When the study group is a select one, the control group must have the same composition. In the example cited, a group with localized disease treated with roentgenotherapy could be used as a control.

Observations. Records should include each manifestation of the disease and should indicate how each manifestation changes with therapy. The date, site and type of recurrence should be recorded. If the patient has had previous therapy, the response to that therapy should be stated since the use of a new agent in therapy-resistant patients is a more severe test than the use in therapy-sensitive patients. If the new agent has no effect but subsequent therapy of another type is effective, this observation should be included. For example, Alpert et al.[20] reported cases in which lymphadenopathy did not completely regress or promptly recur after HN_2 therapy. The same patients received a much better and longer lasting effect from subsequent roentgenotherapy. The inclusion of their results with the roentgenotherapy gave valuable information regarding the effect of HN_2 on lymphadenopathy which would have been missed if the report had included only the effect of the new drug being tested.

Duration of Study. When the objective of the study is a limited one, such as testing the effect of a drug on the fever in patients with Hodgkin's disease, the cases need only be followed until the drug has had time to act. When it is desired to determine whether or not a new agent will prolong life, a long period of observation is necessary. At present, 40 to 60 per cent of the patients will have run the course of the disease

within three years, and probably a minimal follow-up of three years would give an indication of any effect on survival. In general, of course, the longer the follow-up the better. However, it is difficult to keep therapy uniform for long periods.

Measurement of Results and Reporting of Data. The selection of a yardstick for measurement of results becomes a problem only when one is attempting to determine the effect of an agent on the overall course of the disease. Yearly survival, mean survival and five-year survival each have been used frequently as a sole measure of the results of therapy. All have limitations. Five-year survival does not reflect cure of lymphoma since patients frequently relapse after a "disease-free" remission of more than five years, and some patients survive for more than five years without ever losing all evidence of the disease. The five-year survival rate does not measure any of the effects of therapy in patients who die in less than five years. If, for example, a new drug doubled the survival of advanced cases destined to die within one to two years, this important fact would be missed if five-year survival were used as the sole measure of results. Mean or median survival rates have limited value in diseases with such a wide range of individual survivals unless the groups of cases are large.

Measurement of survival does not indicate whether the patients received any symptomatic benefit from therapy. The current therapy of lymphomas is not promising in regard to longevity and, consequently, one of the present primary goals of treatment is to give the patient as long a life and as comfortable and useful a one as possible even though he will ultimately die of the disease. The yardstick used to measure results of therapy must give some information regarding the quality of response. In part I of the present study remission after each course of therapy and total period of remission were used to measure results. Remission was defined as the period during which the patient could perform his normal activities with or without objective evidence of disease. Any response of less than one month's duration was not considered a remission. Karnofsky et al.[36] used a performance grading system to measure remission.

Improper methods used to calculate and express the data on results of therapy may produce errors in conclusions. The reference point for the start of a measure of survival or remission must be uniform if different studies are to be compared. The time of diagnosis is preferable to the estimated time of onset in calculating survival. In Table I the survival rates for both the living and dead patients are given separately for several of the studies. In all instances those of the living patients were much better. In Burnam's series the five-year survival was 41 per cent for the living patients and 15 per cent for the dead patients. Obviously, exclusion of the living patients from the calculations of survival, as by Minot and Isaacs[12] and others, significantly altered their findings. Nor should the patients lost to follow-up be excluded from the calculations. The reasons for their disappearance may be related to the results of the therapy; they may have done poorly and sought help elsewhere or may not have returned because they were well. A life table is the best single means of expressing the survival of patients with lymphoma. It gives the yearly survival rates up to the end of the period of study. Living patients and lost patients are indicated, the time of last observations is given and patients are included in the calculations up to the time of last observation. The life table indicates only the quantitative response. A remission table calculated in the same manner as the life table except that end of total remission is used in place of end of life expresses both the qualitative and quantitative results of therapy. An example of such a table, Table III, was calculated from the data in part I of the present study.

The possibility of cure, complete elimination of the disease, has not been included in this discussion of methods. The reader is referred to the papers of Stout[5,11] for an excellent discussion of the determination of cure of a malignant lymphoma. None of the methods of expressing results herein discussed will indicate potential cures. In addition to the life table and remission table, there should be an indication of those patients who have survived for a long period, for example ten years, without any further evidence of disease.

The need for standardization of the methods of the study of the therapy of lymphomas has been presented. Lymphomas are comparatively rare diseases and even large institutions may have difficulty in accumulating a sufficient number of patients in all stages of disease for a proper study. Perhaps both problems could best be overcome by reporting cases to a central agency. This has been done in other fields by the Com-

TABLE III

REMISSION TABLE FOR ALL PATIENTS IN PRESENT SERIES TREATED FOR HODGKIN'S DISEASE*

Post Therapy (yr.) x	No. Present at Beginning of Year lx	No. Last Observed wx	Ended Remission rx	Lost to Follow-up lox	Effective Number Present $lx = \frac{wx}{2} + lox$	Probability of Ending Remission qx	Remaining in Remission (annual %)	Remaining in Remission (cumulative %)
0	64	0	32	0	64	.50	50	..
1	32	0	10	0	32	.33	67	34
2	22	0	1	0	22	.05	95	32
3	21	1	4	0	21	.19	81	26
4	16	1	4	0	16	.25	75	19
5	11	0	4	0	11	.36	64	13
6	7	0	1	0	..	...	..	..
7	6	1	0	0	..	...	..	..
8	5	1	0	0	..	...	..	..
9	4	1	0	0	..	...	..	..
10	3	1	0	0	..	...	..	..

* Based on standard life table, using end of remission in place of end of life on standard table.

mittee on Research of the Council on Pharmacy and Chemistry of the American Medical Association and in the Cooperative Study of the Chemotherapy of Tuberculosis of the Veterans Administration. Pertinent data could be assembled and evaluated, and projected studies could be planned on new drugs that show promise.

CONCLUSIONS

Localized lymphosarcoma and reticulum cell sarcoma are curable in some instances, especially if the primary focus is in a viscus, particularly the stomach or small intestine. There is no conclusive evidence that localized Hodgkin's disease can be cured. Surgery and roentgenotherapy have been equally effective in the treatment of localized lymphosarcoma. Except for these occasional apparent cures there is no proof that roentgenotherapy has prolonged the life of patients with any of the lymphomas, although some data suggest a prolongation of life. One report indicates that in Hodgkin's disease life has been prolonged by vigorous local therapy plus prophylactic therapy to uninvolved areas but the findings must be confirmed by wider use of these methods on all clinical types of Hodgkin's disease. There is no question that treatment results in symptomatic improvement. It is impossible to conclude from existing data what technics of roentgenotherapy are preferable.

Nitrogen mustard gives relief of symptoms and reduces tumors in all types of lymphomas. The duration of remission from a course of HN_2 is less than that obtained by a course of roentgenotherapy but there is insufficient information to permit a comparison of the two agents regarding effect on the overall course of the disease. Roentgenotherapy is more effective in reduction of tumors. Combining the two agents results in more efficient therapy but survival is the same as when roentgenotherapy is used alone.

The therapeutic effect of TEM is similar to that of HN_2 but the depressant effect of the oral form of TEM on the bone marrow is less predictable than that of HN_2. The effect of TEM on survival has not yet been evaluated.

Patients who have advanced disease frequently obtain some symptomatic relief from cortisone or ACTH. These hormones may decrease hemolysis in patients with a secondary hemolytic anemia and may increase hematopoiesis in patients with hypocellular bone marrow.

That definite conclusions cannot now be drawn in respect to the agents discussed is due partly to non-standardized and inadequate methods of study. The establishment of basic principles of methods of study, and better organization of effort would increase the value of future studies.

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Clinical Trial of Glaucarubin in Treatment of Amebiasis*

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COMPOUNDS possessing potent amebacidal properties in experimental amebiasis have recently been isolated from plants of the genus simarouba, in particular from Simarouba amara and S. glauca. One of these fractions, a crystalline glycoside, has been designated glaucarubin.[1] The present paper reports an evaluation of this product in the treatment of acute and chronic amebiasis in man.

Interest in the use of products derived from simarouba in the treatment of amebiasis has ample basis. Extracts from these plants and substances isolated from them have been used clinically at various times. Why they fell into disuse intermittently after encouraging reports appeared from time to time is not clear. The articles of Nixon[2] and of Shepheard and Lillie[3] on the use of Castela nicholsoni are frequently cited. In Mexico the popular use of chaparro amargoso and the development of some commercial products demonstrate the amebacidal activity of such plants. However, a sufficiently pure product of constant activity developed under strict and well controlled conditions has been lacking until the present.

The clinical use of glaucarubin was preceded by the careful and extensive studies of Cuckler[4] not only on its therapeutic value in amebiasis but also on its toxicity and pharmacology in general. The investigations of Cuckler and his collaborators[5] show that, in dogs severely infected with Endamoeba histolytica, repeated oral doses of 0.5 and 2.5 mg./kg. eliminated the amebas between the fifth and the eighth day of treatment. The dogs remained clinically well for more than thirty days and during the same period it was impossible to show the existence of amebas by microscopic study and culture. Autopsy did not reveal amebic infection in any of the dogs treated. A daily oral dose of 10 mg./kg. eliminated the infection in the fourth day of treatment. Frequent examinations over a period of one month revealed nothing pertinent for amebae. One relapse was observed after ten weeks. A single dose of 20 mg./kg. was even more effective. In rats infected with E. histolytica 90 per cent were cured by single oral doses of 100 mg./kg. Single doses of 200 mg./kg. cured 100 per cent of the rats. Incorporation of the drug in the diet at 0.04 per cent given *ad libitum* during six days cured 90 per cent of them. A single oral dose of 6.2 mg./kg. given three hours prior to inoculation will prevent the establishment of amebiasis in the rat. A larger oral dose of 100 mg./kg. also will prevent the development of amebiasis when administered twenty-four hours before experimental inoculation.

In experimental fulminating amebiasis in the guinea pig, Taylor and Greenberg[6] found that glaucarubin was the most effective antiamebic agent in a series of fifty compounds. In a dosage of 10 to 40 mg./kg. for 7 days glaucarubin is curative and well tolerated by the guinea pig. A single oral dose of 140 mg./kg. administered eighteen hours after infection is curative for 50 per cent of the experimental animals.

While determining the lethal dose for different animal species these investigators noted that the rat, mouse, rabbit and chicken tolerated glaucarubin much better than dogs. For mice the LD_{50} was 1,600 mg./kg. in a single oral dose. Rats tolerate glaucarubin in a single oral dose of 6,400 mg./kg. Repeated daily oral doses of 200 mg./kg. (twice a day for fourteen days) have no significant deleterious effect on the growth of young rats and the mortality is negligible (1/20). Daily oral doses of 8 to 32 mg./kg. for ninety-one days had no adverse effect on the growth of rats and no hematologic or pathologic changes were noted during the period of administration or at autopsy. In the

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TABLE I

RESULTS OF TREATMENT OF AMEBIASIS WITH GLAUCARUBIN

Patient and Sex	Age, (yr.)	Daily Dose (mg.)	Days Treated	Total Dosage (mg.)	Results of Parasitologic Examination During Treatment (days)										Symptoms of Intolerance	Results of Parasitologic Examination after Treatment
					1	2	3	4	5	6	7	8	9	10		
S. C., M	22	20	8	160	+	..	+	−	−	−	..	−	..	..	None	.....
L. C. R., F	9	30	8	240	+	+	+	+	..	−	−	−	..	..	None	− After 1 mo.
E. J. M., F	25	10	36	360	+	..	+	+	+	..	+	−	−	+	None	+ After 1 mo.
I. G., F	38	40	21	840	+	..	+	+	+	+	+	..	+	+	None	.....
D. C., F	42	20	8	160	+	+	+	+	+	−	−	−	..	..	None	.....
G. M., F	51	40	13	520	+	+	+	+	..	−	+	+	+	−	None	− After 1 mo.
A. M. L., F	35	40	21	840	+	+	+	+	..	..	..	+	+	+	None	+ After 1 mo.

dog a single oral dose of 400 mg./kg. was lethal after two to three days. A single dose of 100 mg./kg. produced only lack of appetite and a single intravenous dose of 8 mg./kg. lacked noxious effects. The daily oral administration of 2 mg./kg. per day was well tolerated by the dog over eleven weeks (fifty-five doses). In anesthetized dogs doses of 1 to 50 mg./kg. intravenously did not produce any effect on the respiration or the heart and arterial pressure.

Cuckler and Smith[7] indicate that the drug is more potent in animals than many of the commonly used antiamebic agents and, since the therapeutic doses are much smaller than the toxic doses, thus providing an ample margin of safety, they recommended clinical study of the drug in the treatment of human amebiasis.

METHODS

The drug was administered to a total of eighty-seven patients with amebiasis. The laboratory diagnosis of amebiasis was made in the chronic cases (seventy-eight patients) by examining several fecal samples obtained shortly after administration of a saline laxative. In the acute cases (nine patients) the fecal samples were examined immediately after discharge.

The drug was administered orally, dividing the daily dose into three parts. The dosages employed were varied considerably due to our using a new drug and trying to establish an adequate therapeutic dosage. A schedule of 3 mg./kg./day for five days was finally developed. The dosages used for the patients are indicated in Tables I through VI.

The cases of chronic amebiasis were studied in five groups; in the first group of seven patients (Table I) the daily dose varied from ten to forty mg. per patient (0.2 to 1 mg./kg.), the total dose being from 160 to 840 mg. and the days of uninterrupted treatment varying from eight to thirty-six. In the second group of fifteen patients (Table II) the daily dose was thirty mg., and a total dose of 300 mg. was given, the days of consecutive treatment being ten. In the third group of eleven patients (Table III) the daily dose was fifty mg., and a total dose of 500 mg. was administered, the drug being given during ten consecutive days. In the fourth group of seven patients (see Table IV) the daily dose was 200 mg. and the total dose was 1 gm., the days of consecutive treatment were five. In the fifth group of thirty-eight patients (Table V) the daily dose was thirty mg. per ten kg. of weight, and the total dose varied from 200 to 1,400 mg.; the days of consecutive treatment were five. In thirty patients of this group a blood count and differential were obtained before and after treatment.

The study of the patients who had amebic dysentery was made in two groups. In the first, three patients were treated with an initial daily dose of 10 mg. of glaucarubin. In one of these patients the dosage of the drug was gradually increased to 40 mg. and in another to 60 mg. daily. (Table VI.) The total amounts of the drug were 80, 1,190 and 740 mg., and the days of treatment were eight, thirty-two and thirty, respectively. In the second group (Table VI) six patients were treated. In one patient the dose was 200 mg. daily during five consecutive days. In the other five patients the daily dose was fifty mg. This dosage was increased in two patients, in one to eighty mg. and in the other to 200 mg. daily. The total dose varied from 500 to 1,350 mg., and the days of treatment between ten and twenty. In ten of the patients (the majority of whom received treatment for more than two weeks) coagulation and bleeding times were determined; the thymol turbidity, cephalin-cholesterol flocculation, and bromsulfalein retention tests were also obtained before and after treatment.

TABLE II

RESULTS OF TREATMENT OF AMEBIASIS WITH GLAUCARUBIN

Patient and Sex	Age, (yr.)	Daily Dose (mg.)	Days Treated	Total Dosage (mg.)	Results of Parasitologic Examination During Treatment (days)										Symptoms of Intolerance	Results of Parasitologic Examination after Treatment
					1	2	3	4	5	6	7	8	9	10		
F. C. A., F	17	30	10	300	+	+	−	..	−	−	−	−	−	−	None	− After 5 mo.
F. A. C., F	45	30	10	300	+	+	..	−	−	−	−	..	−	−	None	− After 5 mo.
F. A. M., F	51	30	10	300	+	..	+	+	+	+	+	−	−	−	None	− After 1 mo.
M. I. R., F	42	30	10	300	+	..	−	..	−	−	−	..	−	−	None	− After 5 mo.
A. M. C., F	43	30	10	300	+	+	+	−	..	−	−	−	−	−	None	+ After 4 mo.
M. H. G., F	44	30	10	300	+	+	+	+	..	−	−	−	..	−	None	− After 1 mo.
M. C. Q., M	18	30	10	300	+	..	−	..	−	..	−	−	−	−	None	− After 1 mo.
P. M. G., F	27	30	10	300	+	+	..	−	−	..	−	−	−	−	None	+ After 1 mo.
F. R. O., M	17	30	10	300	+	..	−	−	−	−	−	−	..	−	None	− After 11 mo.
G. I. R., F	23	30	10	300	+	+	+	−	−	..	−	−	−	−	....	.....
J. G. R., F	23	30	10	300	+	+	+	−	−	−	−	−	−	−	....	.....
E. M. P., F	29	30	10	300	+	+	−	+	−	..	−	−	−	−	None	+ After 2 mo.
J. O. O., F	18	30	10	300	+	+	+	..	−	−	−	−	−	−	None	.....
S. M. P., M	42	30	10	300	+	+	..	−	−	−	−	−	−	−	None	− After 3 mo.
M. A. H., F	52	30	10	300	+	+	+	..	−	−	−	−	−	−	None	.....

TABLE III

RESULTS OF TREATMENT OF AMEBIASIS WITH GLAUCARUBIN

Patient and Sex	Age, (yr.)	Daily Dose (mg.)	Days Treated	Total Dosage (mg.)	Results of Parasitologic Examination During Treatment (days)										Symptoms of Intolerance	Results of Parasitologic Examination after Treatment
					1	2	3	4	5	6	7	8	9	10		
E. R., F	26	50	10	500	+	−	−	−	−	−	−	−	−	−	None	.....
A. R., F	65	50	10	500	+	+	+	−	−	−	−	−	−	−	None	.....
D. O., F	20	50	10	500	+	−	−	−	..	..	..	−	−	−	None	.....
C. R., F	22	50	10	500	+	+	+	+	+	+	−	−	−	−	None	− After 1 mo.
C. M., F	32	50	10	500	+	+	−	−	−	−	−	−	−	−	None	.....
C. R. N., F	21	50	10	500	+	+	−	−	+	+	−	−	−	−	None	.....
G. G., F	34	50	10	500	+	+	+	−	+	+	−	−	−	−	None	.....
J. C., M	26	50	10	500	+	+	+	+	−	..	−	−	−	−	None	.....
F. G., F	28	50	10	500	+	−	..	−	−	..	−	−	−	−	None	.....
I. G. D., M	35	50	10	500	+	−	−	−	−	−	−	−	−	−	None	.....
A. R., F	65	50	10	500	+	+	+	+	+	+	+	+	+	+	None	+ After 1 mo.

RESULTS

At the start of the treatment all of the patients with chronic amebiasis had great quantities of cystic forms of E. histolytica in the feces. No patient could be considered a simple asymptomatic carrier because all of them had, in variable degrees, signs and symptoms of chronic amebiasis. When these patients were subjected to treatment with glaucarubin, clinical improvement was evident in all from the third to the fourth day, including those patients in whom the parasite continued to appear in the feces. Symptomatic improvement persisted after discontinuance of therapy and those patients who were infected only with E. histolytica were completely free of signs. Three patients complained of anorexia and nausea, one had diarrhea. As there were no laboratory indications of toxicity

TABLE IV

RESULTS OF TREATMENT OF AMEBIASIS WITH GLAUCARUBIN

Patient and Sex	Age, (yr.)	Daily Dose (mg.)	Days Treated	Total Dosage (mg.)	Results of Parasitologic Examination During Treatment (days)					Symptoms of Intolerance	Results of Parasitologic Examination after Treatment
					1	2	3	4	5		
L. G. C., F	42	200	5	1,000	+	+	−	−	−	None	− After 3 mo.
S. M. S., F	45	200	5	1,000	+	+	−	−	−	None	− After 1 mo.
G. M. A., F	43	200	5	1,000	+	+	−	−	−	None	− After 2 mo.
C. O. G., F	29	200	5	1,000	+	−	−	−	−	Nausea, anorexia	− After 4 mo.
P. H. L., F	50	200	5	1,000	+	−	−	−	−	Nausea, anorexia	− After 1 mo.
C. M. H., F	40	200	5	1,000	+	−	−	−	−	None	+ After 1 mo.
B. J. M., F	58	200	5	1,000	+	−	−	−	−	Nausea, diarrhea	.....

the drug was not discontinued in these patients. In no instance were toxic reactions of importance observed.

When treatment was started in the acute cases all had the symptoms and signs characteristic of the severe form of amebic dysentery and contained a great number of mobile E. histolytica trophozoites in the feces. In these patients the clinical response to treatment was rapid and spectacular. After twenty-four hours of treatment the frequency of the stools had diminished greatly, as well as the intensity of the tenesmus and abdominal pain. Between the second and the fourth day the mucus and blood disappeared completely from the feces and they were of normal appearance. Two patients whose initial doses were low (Table VI) continued to show traces of mucus and blood intermittently in the feces; this made it necessary to increase the dosage gradually and to prolong days of treatment. Complete remission ultimately was obtained. In two patients, it was necessary to repeat the therapy because relapses occurred six days after the first course of treatment had ended. In one of these patients administration of the same dosage was repeated (Table VI) and the results obtained were again promising. A complete cure was obtained on the sixth day of the second treatment. The other patient relapsed even after an increase of the dose but only a slight remission occurred. It is pertinent that in this case the dose was small (80 mg.) in relation to that used later (200 mg.). In the nine patients in the acute phase of the disease who were treated in this group the tolerance to the drug was excellent. Six of them were followed for periods of one month to one year and during this time no relapses occurred.

In three of seven patients treated in the first group (Table I) stool examinations gave negative results for E. histolytica on the last day (tenth) of treatment. The stools in two of the four remaining patients one month after treatment again became positive for amebae. In the second group (Table II), no cysts were found after two to seven days of treatment in fifteen patients. Observation of eleven of the patients was continued for one to eleven months in which time cysts were found again in only two patients. In the third group (Table III) of eleven patients the parasites disappeared from the feces between the first and seventh day of consecutive treatment. However, in one patient the cysts persisted. Thirty days later the stools of this patient were still positive, while in another of the two cases in which observation was possible in this group the stools gave negative results. In the seven patients of the fourth group (Table IV) the cysts of E. histolytica disappeared from the stools twenty-four or forty-eight hours later. Repeated examinations were carried out for one to four months after treatment in six of these patients and in only one case did cysts reappear. Finally, in the thirty-eight patients of the fifth group (Table V) the stools were negative for the parasite twenty-four and seventy-two hours after treatment had begun; in one patient they were negative the fourth day after treatment had begun. Twenty-five patients of this group were followed for one to thirteen

TABLE V

RESULTS OF TREATMENT OF AMEBIASIS WITH GLAUCARUBIN

Patient and Sex	Age, (yr.)	Daily Dose* (mg.)	Days Treated	Total Dosage (mg.)	Results of Parasitologic Examination During Treatment (days)					Symptoms of Intolerance	Results of Parasitologic Examination after Treatment
					1	2	3	4	5		
L. B. M., F	44	200	5	1,000	+	+	−	−	−	None	− After 1 mo.
R. P. M., F	15	130	5	650	+	..	−	−	−	None	− After 1 mo.
I. S. T., F	38	140	5	700	+	..	−	−	−	None	.....
J. A. A., M	49	150	5	750	+	+	−	−	−	None	.....
O. G. E., M	63	280	5	1,400	+	..	−	−	−	None	− After 1 mo.
T. R. P., M	38	200	5	1,000	+	+	+	−	−	None	.....
F. M. E., M	35	160	5	800	+	+	+	−	−	None	.....
M. M. G., F	52	200	5	1,000	+	+	−	−	−	None	.....
R. L. T., F	50	150	5	750	+	−	..	−	−	None	.....
C. A. M., F	19	150	5	750	+	+	..	−	−	None	− After 1 mo.
M. G. C., F	27	150	5	750	+	+	+	−	−	None	− After 1 mo.
M. H. R., F	55	200	5	1,000	+	+	..	−	−	None	− After 1 mo.
M. C. S., F	22	160	5	800	+	..	−	−	−	None	− After 1 mo.
R. C. Q., M	23	140	5	700	+	..	−	−	−	None	− After 1 mo.
Y. M. M., F	16	140	5	700	+	+	−	−	−	None	− After 1 mo.
M. A. M., M	15	140	5	700	+	−	−	−	−	None	− After 1 mo.
M. S. P., F	33	180	5	900	+	+	..	−	−	None	− After 1 mo.
J. V. H., F	55	120	5	600	+	−	−	−	−	None	− After 1 mo.
G. M. F., M	18	160	5	800	+	..	−	−	−	None	− After 2 mo.
J. M. M., F	32	140	5	700	+	+	−	−	−	None	− After 1 mo.
C. T. A., F	33	150	5	750	+	+	+	+	−	None	.....
M. M. M., M	5	50	5	250	+	+	−	−	−	None	− After 1 mo.
C. M. R., M	2.7	40	5	200	+	+	−	−	−	None	− After 1 mo.
M. A. P., M	18	160	5	800	+	−	−	−	−	None	− After 1 mo.
T. T. G., F	58	200	5	1,000	+	−	−	−	−	None	− After 2 mo.
M. O. M., F	44	200	5	1,000	+	+	..	−	−	None	+ After 3 mo.
A. N. V., F	18	160	5	800	+	−	−	−	−	None	.....
M. P. G., F	48	200	5	1,000	+	−	..	−	−	None	.....
E. S. M., M	12	100	5	500	+	+	−	−	−	None	− After 13 mo.
M. R. A., F	26	140	5	700	+	+	+	−	−	None	.....
M. R. P., F	46	180	5	900	+	−	..	−	−	None	.....
J. S. C., F	21	150	5	750	+	−	..	−	−	None	− After 3 mo.
G. G. R., F	23	180	5	900	+	+	−	−	−	None	− After 5 mo.
F. R. P., F	33	160	5	800	+	−	..	−	−	None	− After 4 mo.
E. O. H., F	42	170	5	850	+	−	..	−	−	None	.....
J. J. G., F	43	200	5	1,000	+	−	−	−	−	None	− After 3 mo.
A. G. H., F	25	140	5	700	+	..	−	−	−	None	− After 2 mo.
R. N. D., F	11	40	5	200	+	+	..	−	−	None	.....

* 30 mg./10 kg. weight

months; only one case relapsed, reappearance of cysts in the feces occurred during this period. Blood counts and differentials in thirty patients of this group showed no noteworthy changes after treatment.

In these patients, in the acute phase (Table VI) stools examinations were negative for E. histolytica on the second to the twenty-sixth day after treatment. Of the nine patients treated in this group six were followed for one to thirteen months, in which period no relapses were recorded. In one patient E. histolytica trophozoites continued to appear in the feces and, because clinical improvement was poor, treatment was stopped. Liver and kidney function tests made in ten patients before and after treatment did not show changes in any case, in spite of prolonged treatment, from fifteen to thirty-six consecutive

TABLE VI

RESULTS OF TREATMENT OF ACUTE AMEBIASIS WITH GLAUCARUBIN

Patient and Sex	Age (yr.)	Days Treated	Total Dosage (mg.)	Daily Dose (mg.)	Results of Parasitologic Examination During Treatment (days)													Clinical Improvement	Results of Parasitologic Examination After Treatment
					1	2	3	4	5	6	7	8	9	10	11	12	13		
M. G. R., F	6	8	80	10	+	−	+	−	−	−	−	−	..	..	..	..	..	Complete	.....
J. E. N.,* F	24	32	1,190	10	+	+	−	−	..	..	..	..	..	..	..	..	..	.....	
				20	+	+	..	−	..	−	−	−	..	..	..	..	..	.....	
				40	+	+	..	−	..	−	−	..	..	..	..	..	..	Complete	.....
				50	+	+	−	+	−	..	+	..	..	..	..	..	..	.....	
				60	−	−	−	−	−	−	..	..	..	..	..	..	..	.....	
H. P. N.,* F	27	30	740	10	+	+	+	+	+	..	−	−	+	+	..	..	..	.....	
				20	+	+	..	+	+	+	+	+	..	..	..	..	..	Complete	− After 1 mo.
				40	+	−	−	−	−	..	−	−	..	−	−	−	..	.....	
M. B. H., F	43	10	500	50	+	+	−	−	−	−	..	−	−	−	..	..	..	Complete	− After 1 mo.
A. P. B., M	28	10	500	50	+	+	..	−	−	−	−	−	−	−	..	..	..	Complete	− After 12 mo.
J. M. Z., M	30	20	1,000	50	+	+	+	−	−	−	−	−	−	−	..	..	..	.....	
				50	+	+	..	+	+	−	−	−	−	−	..	..	..	Complete	− After 1 mo.
J. C. E.,* M	32	18	1,140	50	+	+	+	+	+	+	..	−	−	−	..	..	..	.....	.....
				80	+	+	+	..	+	+	+	+	..	..	..	..	..	Slight	
D. C. R.,* F	30	12	1,350	50	+	+	+	−	−	+	+	..	..	..	..	..	..	.....	
				200	+	..	−	−	−	..	..	..	..	..	..	..	..	Complete	− After 13 mo.
T. C. X., F	22	5	1,000	200	+	+	−	−	−	..	..	..	..	..	..	..	..	Complete	− After 3 mo.

* The doses were increased by steps, that is, the new dosage was administered after the previous one.

days, to which seven of these patients were submitted, and despite the comparatively large doses used.

SUMMARY AND CONCLUSIONS

Seventy-eight patients with chronic amebiasis (E. histolytica cysts) and nine patients with amebic dysentery (vegetative forms of the parasite) were treated with glaucarubin, a crystalline glycoside derived from simarouba. The patients were studied in six different groups. The daily dose varied from 10 to 280 mg. and the duration of treatment varied from five to thirty-two consecutive days.

Clinical improvement was evident from the first to the sixth day after treatment had begun. No toxic symptoms were noted and the drug was well tolerated. Parasitologic examinations of the stool gave negative results as early as the first day of treatment; in only two patients did the parasites persist. No changes were detectable in blood counts and differentials in thirty-six patients or in liver function tests which were performed on ten patients before and after treatment. After treatment was terminated fifty-four patients were observed for a period of one to thirteen months. Eight of the patients with chronic amebiasis developed recurrence of E. histolytica.

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Review

Serologic Tests for Inflammation*

Serum Complement, C-reactive Protein and Erythrocyte Sedimentation Rate in Myocardial Infarction

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NON-SPECIFIC tests which reflect inflammation are in common usage as aids in the diagnosis and management of various diseases. Inflammatory reaction following myocardial infarction has been well documented by manifestations of fever and leukocytosis. In the serum many changes occur, the most widely appreciated being those which result in an increased erythrocyte sedimentation rate.

In 1943 Lofstrom reported that seven patients with myocardial infarction demonstrated a substance in their sera which caused the non-specific swelling reaction of pneumococci.[1] The substance causing this reaction was later identified[2] with the C-reactive protein which Tillett and Francis[3] originally described in various febrile infectious conditions. Since then a number of studies have confirmed the appearance of C-reactive protein in myocardial infarction and other non-infectious inflammatory conditions.[4–6]

Changes in serum complement (C′) have also been identified with infectious conditions.[7] Previous studies[8,9] have shown that the concentration of C′ may increase remarkably in non-infectious conditions such as carcinomatosis or myocardial infarction. Thus in addition to the specific fixation or decrease of C′ which may occur *in vivo* with antigen-antibody reactions such as serum sickness[10] and acute nephritis,[11,12] C′ may increase as a result of a wide variety of inflammatory conditions.

This report is concerned with the simultaneous serial determination of three tests of inflammatory reaction: the erythrocyte sedimentation rate (ESR), the C-reactive protein test (CRP), and the determination of serum complement (C′) in myocardial infarction. Since myocardial infarction usually has an abrupt onset which can be readily timed, an attempt was made to appraise the efficacy of these tests early in the course of the disease and during the recuperative period when inflammation is subsiding.

METHODS

Fifty-nine patients with presumed myocardial infarction were selected for study at the Bronx Hospital and at the Presbyterian Hospital. Blood was obtained periodically for the determination of the erythrocyte sedimentation rate and for the collection of serum. Serum was stored at −50°C. until the complement determination and C-reactive protein test were performed.

Clinical measures indicated by the patient's condition were instituted, usually including analgesics and anticoagulants, and occasionally including oxygen, digitalis and mercuhydrin therapy. None of these measures appeared to influence these tests in this or previous studies.

The ESR was performed by the Westergren method. (Refer to ref. 13.) A sedimentation rate greater than 10 mm. in sixty minutes is considered abnormal in this study. The normal range found by Westergren was 1–3 mm. for males and 4–7 mm. for females.[13] In previous studies in rheumatic fever we have been impressed with the regularity with which the ESR returns to less than 8 mm. in the follow-up period of patients who have had no persistent rheumatic activity. Frequently blood for a simultaneous sedimentation rate by the Wintrobe method was also obtained and the hematocrit determined for corrections as recommended. (Refer to ref. 13.) Usually the

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TABLE 1

CUMULATIVE POSITIVE TESTS FOR INFLAMMATION IN MYOCARDIAL INFARCTION OCCURRING IN FIFTY-NINE PATIENTS*

	"Definite" Infarction					"Probable" Infarction					"Possible" Infarction				
Days	1	2	3–4	5–7	8+	1	2	3–4	5–7	8+	1	2	3–4	5–7	8+
No. of infarctions	15	17	26	39	46	3	2	4	5	5	1	1	3	5	6
C′ > 45	13	14	25	39	45	1	2	4	5	5	0	1	3	5	6
CRP 1+ or >	13†	16†	23†	36†	43†	1	0	3	4	5	1	1	3	4	5
ERS (Westergren) >10	7	13	24	35	43†	0	1	4	5	5	0	1	3	5	5

* Four patients had at least one negative test and no late determinations.
† One value missing.

serial results of the Westergren and Wintrobe methods were of similar order in the lower ranges. Because there is a greater range of values possible with the Westergren method, and because it appears to have greater reproducibility and simplicity, it has been used in this study to compare the ESR with the C′ and CRP tests.

Sera were analyzed for the presence of C-reactive protein by the capillary precipitation method of Anderson and McCarty,[14] employing rabbit anti-CRP antiserum initially obtained through the courtesy of Drs. Harrison Wood and Maclyn McCarty of the Rockefeller Institute, New York, and later from commercial sources. Rabbit antiserum was drawn into a capillary tube and then allowed to mix with a patient's serum. The capillary tubes were incubated at 37°c. for two hours, and refrigerated at 4°c. overnight; controls containing unmixed patient's serum were similarly treated. No visible precipitate and equivocal amorphous aggregates (±) were considered negative tests. Precipitates of characteristic ground-glass appearance were graded one to four plus. Normally no C-reactive protein is present in serum by this technic. It appears in the course of inflammatory reaction due to diverse causes.[14,15]

Serum complement was determined by the spectrophotometric method of Mayer, Osler, Bier and Heidelberger[16,17] using Mg^{++} and Ca^{++} and a final volume of 7.5 cc., as previously summarized.[9] Fifty normal human individuals were found to have 37.7 ± 3.9 50 per cent hemolytic units per ml. of serum[9] and since that time an analysis of thirty-four additional normal persons corroborates the narrow range in normal subjects. Values over forty-five are considered elevated in this study.

Fifty-nine patients were studied. Fifty-five had serial tests; four had single determinations. Two patients had a second episode of myocardial infarction during hospitalization, making a total of sixty-one infarctions in fifty-nine patients. Forty-eight of the patients were men, ages thirty-eight to eighty-two, median age fifty-eight; eleven were women, ages forty-five to seventy-two, median age sixty-one. There were nine deaths (15 per cent) in the series. In three instances autopsies were performed which confirmed the diagnosis of myocardial infarction.

In order to evaluate the data more critically an attempt was made to separate patients with "definite" myocardial infarction from what might be arbitrarily classified as "probable" or "possible" infarction. An instance of myocardial infarction was recorded as "definite" when a characteristic clinical picture with pain, dyspnea or shock was supported by typical and progressive ECG changes. The infarct was still considered definite if these ECG changes were not present or if there were only T wave abnormalities and the clinical findings included the typical pain pattern and two of the following: fever, leukocytosis or a rising ESR. Fifty of the sixty-one episodes studied were considered definite myocardial infarcts.

Cases were classified somewhat arbitrarily as probable (five instances) or possible (six instances) when the total picture was still highly suggestive of infarction but fewer diagnostic criteria were present. When any doubt existed, the less certain category was chosen for the purpose of this study. For clinical purposes, however, all patients appeared to have had myocardial infarction and were so treated by their respective physicians.

RESULTS

Table 1 summarizes the total experience with the tests in sixty-one episodes of myocardial infarction. A positive test in an individual is included in the cumulative total of positive tests with the passage of time although it may subsequently revert to normal. Four patients had at least one negative test and no late determinations. It is readily apparent that after the first two days the percentage of cumulative abnormal results in each of the three tests (C′, CRP and ESR) is well over 90 per cent and there is no obvious difference in the number of positive reactions.

TABLE II

FIRST WEEK RESULTS OF THE PATIENTS WITH INITIAL DETERMINATIONS WITHIN FORTY-EIGHT HOURS

Case No. and Patient	Diagnostic Category	Test†	Day 1			Day 2			Day 3	Day 4	Days 5–7
			8 hr.	16 hr.	24 hr.	32 hr.	40 hr.	48 hr.			
1, C. W.	Definite	C′	36	..	46	....	....	....	..	....	69
		CRP	0	..	3	....	....	....	..	....	3
		ESR	1	..	2	....	....	....	..	....	33
2, J. N.	Probable	C′	43	..	..	....	....	....	64	81	69
		CRP	0	..	..	....	....	....	3	3	0
		ESR	3	..	..	....	....	....	28	28	6
3, E. L.	Definite	C′	53	42	..	....	....	....	80	.....	.....
		CRP	2	3	..	....	....	....	3	.....	.....
		ESR	25	27	..	....	....	....	37	.....	.....
4, E. P.	Definite	C′	..	47	..	....	67	....	..	....	68
		CRP	..	0	..	....	3	....	..	....	3
		ESR	..	6	..	....	9	....	..	....	34
5, I. L.	Definite	C′	..	67	..	....	50	....	..	....	65
		CRP	..	3	..	....	3	....	..	....	3
		ESR	..	25	..	....	28	....	..	....	28
6, J. L.	Definite	C′	..	54	58	....	71	....	..	....	49
		CRP	..	3	3	....	3	....	..	....	3
		ESR	..	10	8	....	10	....	..	....	10
7, I. G.	Possible	C′	..	44	..	....	....	....	..	50	54
		CRP	..	3	..	....	....	....	..	2	0
		ESR	..	2	..	....	....	....	..	3	5
8, I. R.	Definite	C′	..	..	42	....	....	52	..	....	58
		CRP	..	..	2	....	....	3	..	....	2
		ESR	..	..	8	....	....	16	..	....	12
9, I. C.	Probable	C′	..	..	42	....	....	....	..	55	46
		CRP	..	..	3	....	....	....	..	2	3
		ESR	..	..	46	....	....	....	..	46	48
10, S. W.	Definite	C′	..	..	49	....	....	51	..	....	62
		CRP	..	..	3	....	....	3	..	....	3
		ESR	..	..	42	....	....	48	..	....	55
11, J. L.	Definite	C′	..	..	53						
		CRP	..	..	3	Died	....	....	..	....	.....
		ESR	..	..	9						
12, H. B.	Definite	C′	..	..	37						
		CRP	..	..	1	Died	....	....	..	....	.....
		ESR	..	..	4						
13, J. M.	Definite	C′	..	..	51	....	....	....	..	....	.....
		CRP	..	..	3	....	....	....	..	....	.....
		ESR	..	..	15	....	17	....	..	....	25
14, A. B.	Definite	C′	..	..	46	....	....	....	..	....	53
		CRP	..	..	2	....	....	....	..	....	2
		ESR	..	..	16	....	....	....	..	....	41

TABLE II (*Continued*)

Case No. and Patient	Diagnostic Catagory	Test†	Day 1			Day 2			Day 3	Day 4	Days 5–7
			8 hr.	16 hr.	24 hr.	32 hr.	40 hr.	48 hr.			
15, S. M.	Definite	C′	..	..	46	....					
		CRP	..	..	2	....	Died	....	..	....	.....
		ESR	..	..	4	....					
16, L. L.	Definite	C′	..	..	54	....	....	....	..	....	73
		CRP	..	..	..	....	....	....	..	....	1
		ESR	..	..	10	....	....	....	..	....	87
17, S. S.	Definite	C′	..	..	70	....	....	64	..	....	75
		CRP	..	..	3	....	....	3	..	....	3
		ESR	..	..	35	....	....	55	..	....	77
18, R. B.	Definite	C′	..	..	4	....	....	....	..	59	67
		CRP	..	..	3	....	....	....	..	3	2
		ESR	..	..	18	....	....	....	..	85	84
19, J. F.	Probable	C′	..	..	51	....	65	....	..	62	72
		CRP	..	..	0	....	0	....	..	2	2
		ESR	..	..	6	....	5	....	..	9	14
20, M. A.	Definite	C′	..	..	..	75	....	....	..	....	62
		CRP	..	..	..	2	....	....	..	....	3
		ESR	..	..	..	18	....	....	..	....	28
21, D. F.	Definite	C′	..	..	..	....	48	....	..	39	40
		CRP	..	..	..	....	4	....	..	2	2
		ESR	..	..	..	....	13	....	..	43	35
22, F. K.	Definite	C′	..	..	..	....	48	....	..	....	42
		CRP	..	..	..	....	2	....	..	....	2
		ESR	..	..	..	....	11	....	..	....	15
23, V. R.	Definite	C′	..	..	..	....	....	43	..	....	60, 59
		CRP	..	..	..	....	....	2	..	....	1
		ESR	..	..	..	....	....	4	..	....	27, 29
24, J. E.	Probable	C′	..	..	..	....	....	>45	..	>46	.....
		CRP	..	..	..	....	....	0	..	0	.....
		ESR	..	..	..	....	....	14	..	18	.....
25, H. K.	Definite	C′	..	..	..	....	....	36	..	....	53
		CRP	..	..	..	....	....	2	..	....	1
		ESR	..	..	..	....	....	17	..	....	15
26, G. D.*	Definite	C′	..	..	..	....	....	59	..	44	46
		CRP	..	..	..	....	....	3	..	3	3
		ESR	..	..	..	....	....	16	..	46	38
27, I. F.	Possible	C′	..	..	..	....	....	57	..	67	87
		CRP	..	..	..	....	....	2	..	3	2
		ESR	..	..	..	....	....	43	..	82	80

* These determinations occurred during a second infarct while patient was under hospital care.

† C′ = serum complement—(50% units per ml. serum); CRP = C-reactive protein—(graded 0 to 4+); ESR = erythrocyte sedimentation rate, Westergren, (mm. fall after one hour).

Table II lists the results of the tests during the first week in the twenty-seven patients who had tests performed within forty-eight hours after the apparent onset of illness. Three patients were studied within eight hours after onset. In two of the patients all three tests C′, CRP and ESR, were negative. In the third patient all three tests were abnormal. This patient had had an upper respiratory tract infection for a few days and the pharynx was hyperemic on admission. The presence of the positive tests at eight hours may have been related to this inflammatory reaction rather than to the myocardial infarct. In four additional patients tests were made by the sixteenth hour, at which time there were three positive CRP tests, three elevated C′ values and one elevated ESR. By the twenty-fourth hour, of fifteen definite infarcts, thirteen C′ and CRP (one CRP value missing) and seven ESR tests gave positive results. At this time there were relatively fewer positive results in all tests in patients with probable and possible infarcts. By the forty-eight hour period the percentage of abnormal sedimentation rates approximates that of the other tests. The number of positive results in the probable and possible group has also increased. Of forty-nine patients in the three diagnostic groups tested through the first week of illness there were none with normal C′, three with negative CRP tests, and four with normal ESR values. Six of these seven negative values were in patients in the definite group. Only one patient (not seen within forty-eight hours) had both normal CRP and sedimentation rate. The patients with normal CRP tests had no feature in common that could offer an explanation for the negative result. Of the four patients with normal sedimentation rates, two were in congestive failure and in one an elevated ESR developed after the first week.

It was also of interest to determine when the abnormal tests reverted to normal, and this is summarized in Table III. The frequency of persistently abnormal tests at the time of discharge, three to seven weeks after onset, is also listed. In two cases the CRP became negative by the end of the first week. During the second week CRP became normal in six of forty-four cases; ESR, in three of forty-four cases; and C′, in only one of forty-seven cases. The CRP tends to become normal earlier than the other tests and in some instances does so at a time when continued changes in the ECG are occurring (see Cases 10, 23 and 8). In almost all instances, when the CRP became normal, it did so before the other two tests. At the end of hospitalization (three to seven weeks for most patients) approximately half of the CRP tests and only one-third of C′ and ESR tests had returned to normal values. Thus a large proportion of patients were discharged from the hospital with serologic evidence of persistent inflammation which may, however, be of little clinical importance.

TABLE III
REVERSION TO NORMAL AFTER A POSITIVE TEST FOR INFLAMMATORY REACTION IN MYOCARDIAL INFARCTION

Test	Week						No. of Reversions to Negative before Time of Discharge
	1	2	3	4	5	6	
C′	0/47	1/47	5/46	4/32	1/14	0/6	11/47
CRP	2/46	6/44	7/34	7/26	1/12	1/3	24/46
ESR	0/44	3/44	5/41	3/31	0/14	0/4	11/44

Numerator: No. of tests becoming negative.
Denominator: No. of patients under observation with previously positive tests.

CASE REPORTS

CASE 1. C. W. (No. 280545), a sixty-eight year old man, experienced severe chest pain six hours prior to admission. He was acutely ill at the time he entered the hospital (January 12, 1955). The blood pressure was 110/60 and there were crepitant rales at the pulmonary bases posteriorly. Certain aspects of his clinical course are illustrated in Figure 1. The temperature was elevated for eight days, with a maximum of 102°F. on the third day. The leukocyte count was normal on the first day. The electrocardiogram showed progressive changes typical of an acute anterior wall infarct. On the third hospital day symptoms and signs of pulmonary infarction developed suddenly.

Within eight hours of onset the C′ was 36 units, CRP was negative, and the Westergren sedimentation rate was 1 mm., all normal. Sixteen hours later, that is, twenty-four hours after onset, C′ rose to 46 units and CRP became 3+. The ESR became elevated subsequently. C′ rose to very high levels with a peak of 83 units on the tenth day. Part of this rise may be ascribed to the complicating pulmonary infarct.

On the twelfth hospital day severe diarrhea and a temperature of 104°F. developed. There were signs of consolidation at both pulmonary bases. The C′ and CRP were already markedly abnormal; no change occurred in these tests. The ESR curve continued

between 15 and 12 mm. It returned to normal at the beginning of the third week. C′ and CRP continued to be abnormal. Toward the end of the hospital course C′ rose to high levels. This was followed by another febrile episode of obscure origin.

Comment. This is an example of the development of a positive CRP and an elevation of C′ within twenty-four hours of onset of myocardial infarction. The tests at eight hours from onset were normal. The ESR rose subsequently. The course was complicated by pulmonary infarction and severe diarrhea with pyrexia. At the time of discharge, the ESR had returned to normal but C′ and CRP continued abnormal. Contrary to the usual pattern observed, the CRP test was not the first to return to normal. The late rise in C′ during the fourth week will be discussed subsequently.

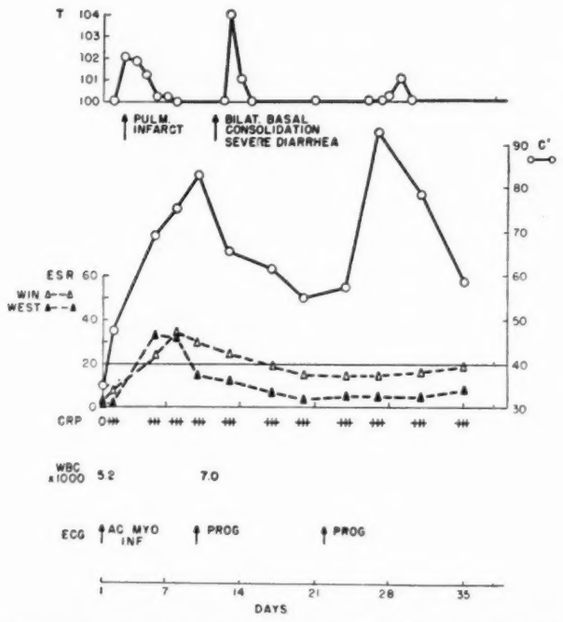

FIG. 1. Case 1. Patient C. W. Chest pain six hours before admission.

CASE 10. S. W. (No. 277741), a fifty-six year old man, developed severe pain in both shoulders radiating down the arms and to the back twelve hours prior to admission (October 16, 1954). Physical examination was not remarkable. The temperature rose to 101°F. and 101.4°F. on the second and third day, respectively. (Fig. 2.) The white blood cell count was 14,000 with 92 per cent neutrophils. On the third day the electrocardiogram showed classic changes of an acute lateral wall myocardial infarction (Q wave in leads I and aVL; S-T segment elevated in leads I, aVL and V_5; biphasic T in leads I, aVL and V_5) and progressive changes occurred on serial tracings. The patient was treated with anticoagulants, analgesics and sedatives, and kept at bedrest for twenty-six days. The course was uneventful and the patient was discharged on the thirty-first hospital day.

The first serologic studies were performed four days after onset. CRP was 4+, C′ was elevated to 57 units, and the Westergren sedimentation rate was 15 mm. The sedimentation rate subsequently rose to a maximum of 51 mm. on the tenth day and gradually returned to below 10 mm. by the twenty-fifth day. The sedimentation rate measured by the Wintrobe method showed corresponding changes. CRP became negative on the fourteenth day at a time when the electrocardiogram continued to show progressive inversion of T waves. C′ returned to a near normal level by the twenty-second day followed, however, by a transient rise during ambulation.

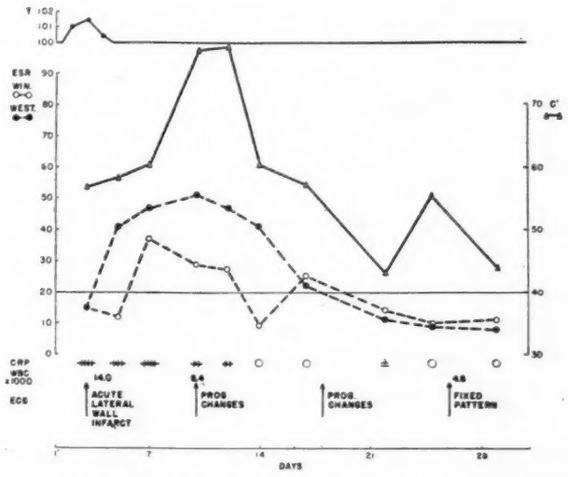

FIG. 2. Case 10. Patient S. W. Chest pain twelve hours before admission.

Comment. In response to the inflammation evoked by myocardial infarction, all three tests studied (C′, CRP and ESR) became abnormal, as did the temperature and white blood cell count. Of the serologic tests, CRP was the first to return to normal, while T wave changes progressed. In this instance C′ and ESR rose and fell in close association. The transient rise of C′ at the time of ambulation is encountered rather frequently in this series. It is not readily ascribable to any new inflammatory process but may be coincident with subclinical effects of increased physical activity.

CASE 23. V. R. (No. 277978), a man of forty-nine years, had an initial episode of angina pectoris for ten minutes one week prior to admission. The pain returned with greater severity one day before admission and persisted until entry into the hospital (October 24, 1954). The blood pressure was 125/80. On auscultation, the heart was normal and the lungs clear. The course is presented graphically in Figure 3. The temperature rose above 100°F. for three days, with a maximum of 100.6°F. The initial leukocyte count was 13,000 with 76 per cent neutrophils. The

electrocardiogram showed Q waves, S-T segment elevation, and T wave inversion in leads II, III, aVF, and T inversion also in V_5 and V_6, indicative of an acute posterolateral wall myocardial infarction. Sedatives and anticoagulants were administered. The patient was discharged after an uneventful four weeks in bed.

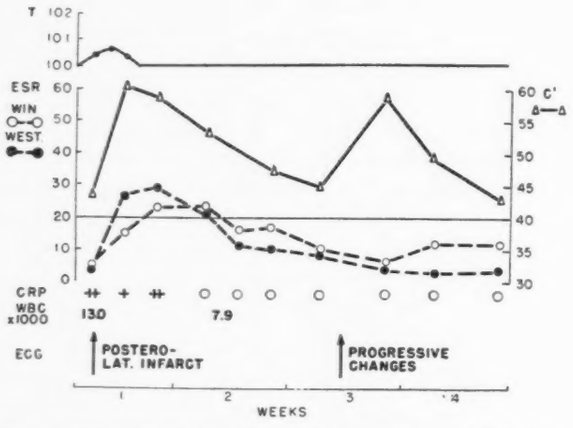

FIG. 3. Case 23. Patient V. R. Chest pain one day before admission.

The initial serologic tests forty-eight hours after the onset showed a positive CRP and normal C′ and ESR. The latter tests were abnormal forty-eight hours later. CRP became negative by the ninth day at a time when the ECG was "evolving" with a return of the S-T segment to the isoelectric line and progressive inversion of T waves. C′ and ESR returned to normal more slowly. A transient rise in C′ recurred toward the end of the hospital course at the time of ambulation.

Comment. In this instance, CRP was the first serologic test to become positive. It also became negative earlier then the C′ and ESR at a time when inflammatory changes were presumably continuing in the myocardium.

CASE 8. I. R. (No. 278711), a sixty-three year old man, had three episodes of angina pectoris during the week preceding hospitalization. Six hours prior to admission (November 15, 1954), moderately severe substernal pain developed which was relieved by an injection of morphine. Physical examination was not remarkable. The course is charted in Figure 4. On the second day the temperature rose to 100.4°F. and the leukocyte count was 10,000 cells per cu. mm. with 69 per cent neutrophils. The initial electrocardiogram showed S-T depression in leads I, II, aVL and V_5 and a biphasic T in aVL. Asymmetric T inversion developed in leads I, II, aVL, aVF and V_5 in serial tracings. The patient was treated with anticoagulants, analgesics, sedatives and bedrest for three weeks, and was discharged after an uneventful course.

Initial serologic determinations were obtained twenty-four hours after the onset of severe pain. (Fig. 4.) The C′ and ESR were within normal limits but the CRP was positive. CRP returned to normal on the eighth day. C′ became elevated forty-eight hours after the onset of illness and returned to normal on the nineteenth day. The ESR showed only a transient and mild elevation.

Comment. In this instance the CRP again was the first test to become positive and the first to return to

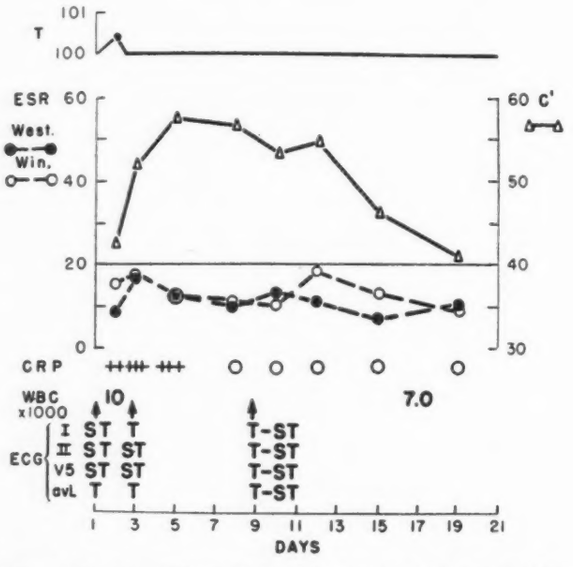

FIG. 4. Case 8. Patient I. R. Chest pain six hours before admission.

normal. It became normal at the beginning of the second week, before the electrocardiogram stabilized. C′ showed a substantial and sustained elevation before returning to normal levels. Although the Westergren sedimentation rate showed only a transient elevation, this is not the usual pattern observed.

CASE 26. G. D. (No. 276996), a forty-eight year old man, was previously hospitalized on two occasions with myocardial infarctions. He awakened on the morning of admission (September 23, 1954) with severe pain radiating to both arms. Nitroglycerin afforded partial relief. The pain became more severe several hours later but disappeared completely fifteen minutes after a nitroglycerin tablet was administered. There were no unusual findings on physical examination, nor was the temperature or white blood cell count increased. The initial electrocardiographic tracing showed evidence of an old anterior wall infarction and S-T and T changes in the chest leads suggesting the possibility of a superimposed acute infarction. A second tracing four days later showed isoelectric S-T segments and upright T waves in the chest leads. The patient was given anticoagulants, analgesics and sedatives. He remained asymptomatic. On the fourteenth hospital day dicumarol was discontinued. Three days later severe substernal constricting pain developed accompanied with fever, leukocytosis and T inversion in leads II, III and aVF.

These electrocardiographic changes were interpreted as those of an acute posterior wall infarction. A pulmonary infarction apparently occurred at the same time, as indicated by the occurrence of hemoptysis. Dicumarol was reinstituted. The patient subsequently improved and was discharged asymptomatic on the forty-fourth hospital day.

The complex clinical course and related laboratory studies are shown in Figure 5. The first period of the hospital course was marked by a positive CRP, elevated C′ and normal ESR. The first two tests indicated organic inflammatory changes in spite of the absence of fever, leukocytosis and progressive electrocardiographic changes. The simultaneous development of infarction of the myocardium and pulmonary embolization on the seventeenth hospital day was accompanied by an unusual and unexplainable initial decrease of C′. An increase of C′ occurred later. CRP continued to be positive. The patient was seen one month after discharge and was asymptomatic. At this time the C′ was 50 units, CRP was 3+ and the Westergren ESR was 22 mm.

Comment. The initial history and course were consistent with a clinical diagnosis of acute coronary insufficiency. The C′ and CRP attest to the presence of inflammation, presumably due to a small acute myocardial infarction. The second period of the patient's hospitalization was marked by overt myocardial infarction and a simultaneous pulmonary infarct. Both pathologic conditions are usually associated with positive C′, CRP and ESR tests.[8] The one month follow-up suggested that the inflammatory response of either or both pathologic conditions, or of an unassociated one, had not yet completely subsided, although the patient appeared well and was asymptomatic.

DISCUSSION

Serologic changes associated with myocardial infarction have been studied by a variety of methods. Alterations have been described in the ESR,[18,19] Weltmann coagulation band,[20] serum glucosamine,[21,35] serum polysaccharides,[22] serum mucoproteins,[23] plasma protein electrophoretic pattern,[24] plasma fibrinogen,[25] serum C-reactive protein,[1,4–6] serum transaminase[26] and serum copper.[27] For the most part these abnormalities are non-specific for myocardial infarction and occur in other conditions associated with tissue damage and inflammation, i.e., pneumonia, peritonitis, rheumatic fever and carcinomatosis.

To this group of acute phase phenomena may be added an increase in serum complement (C′). Serum complement was originally characterized by its lytic action on sensitized bacteria and sensitized sheep cells. It has usually been associated with infectious or immune phenomena and, indeed, was said to differ from specific antibodies in that it did not increase after infection. With more precise methods[16,17] an increase of C′ has been observed in a variety of conditions.[8] Like the ESR and CRP, it has been a useful guide in the management of rheumatic fever.[9,28]

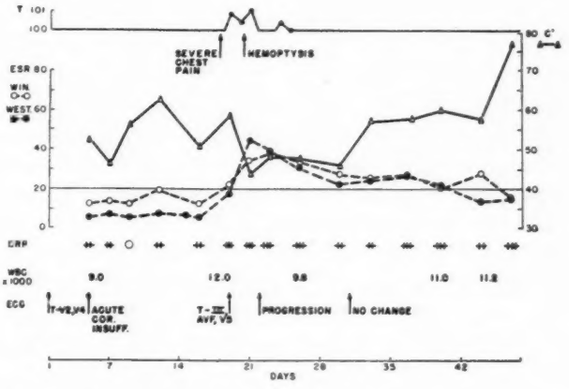

FIG. 5. Case 26. Patient G. D. Chest pain twelve hours before admission.

It is probable that a multitude of reactions occur in serum in the presence of inflammation, irrespective of cause. Many theoretic problems worthy of attention are suggested by the wide variety of chemical aberrations associated with sterile and non-infectious conditions such as myocardial infarction. The role of many of these post-inflammatory reactions or substances is not definable. It appears justifiable to assume that some of these phenomena are not merely the result of waste products of damaged tissue but may represent factors involved in healing or "host resistance."

Certain practical considerations can be defined with greater certainty. Myocardial infarction presents a situation rather ideal for the serial study of acute phase reactions. Its onset is usually abrupt and can be timed with accuracy. After the initial insult healing usually occurs. The acute phase reactions may be compared as to over-all incidence, the rapidity of development of the reaction, and the persistence of positive reactions during the regressive or healing stage. It is apparent from this study that the frequency of cumulative positive reactions in ESR, C′ and CRP tests is not appreciably different on the third day or thereafter. With the criteria used, all three tests gave positive results in well over 90 per cent of the cases and in no patient's serum were the results of all the tests negative simultaneously after the first twenty-

four hours. This is in agreement with reported studies of the sedimentation rate which has been found to be elevated in 90 to 98 per cent of cases.[18,19,29,30] The rapidity with which a positive test developed was also of interest. In the first twenty-four hours abnormal C′ and CRP tests generally appeared while fewer instances of abnormal sedimentation rate are noted. By the forty-eighth hour the difference is no longer appreciable. The CRP test usually becomes negative earlier than the other tests studied. Occasionally it becomes negative during obvious persistence of inflammatory changes as evidenced, for example, by progressive electrocardiographic alterations. The rapid return of the CRP to normal while the ESR is still elevated also occurs in rheumatic fever, as seen in the data of Anderson and McCarty[31] and others.[32,33] Our own observations indicate that the CRP may become normal during persistence of clinical manifestations including polyarthritis and erythema nodosum, at a time when the ESR and C′ continue abnormal.[34]

It is evident, therefore, that with respect to the clinical criteria studied the three tests appear to be of substantially the same value. In occasional instances one or another of the tests may have some superiority. The Westergren sedimentation rate remains a simple, readily reproducible test which allows for more immediate results and interpretation. In a few instances of congestive heart failure or in mild cases of myocardial infarction it may be falsely low. The CRP test is a simple test to perform but requires a preparation of rabbit antibody which may vary in potency and give variable results. Although it may frequently be read within an hour or two, a mildly positive test may not become apparent for twenty-four hours. This test also becomes negative more rapidly than do the others and may perhaps be deceptively normal at a time when inflammatory changes presumably continue. Serum complement also becomes positive early; in addition, it persists abnormal for a longer period of time, more in accordance with the pattern of the sedimentation rate. The C′ test has shortcomings in that it is rather difficult to perform technically, although laboratories performing Wassermann tests may be adapted for this purpose. Increased serum complement as an indication of inflammatory reaction is of interest theoretically in view of the historic association of C′ with "host resistance."[7] It is of more practical diagnostic importance in certain conditions such as acute nephritis[11,12] in which a decreased C′ occurs. For the detection of inflammatory reaction, it would appear that the Westergren sedimentation rate remains the most readily available, easily performed and generally reliable screening test. Like all tests, its reliability is considerably enhanced by careful technic and by serial determinations, particularly with a base line study taken as early as possible in the course of the disease.

In the consideration of the interpretation of all these tests, it should be re-emphasized that they are non-specific and will occur with many inflammatory reactions. Complications such as phlebitis, pneumonia and sinusitis, and congestive heart failure *per se* may give positive reactions on occasion. Of significance, but not considered in this study, is the use of these tests to differentiate uncomplicated angina pectoris from true myocardial infarction. In a few instances in which angina developed late in the course of myocardial infarction the C′, CRP or ESR curves did not appear to be influenced.

SUMMARY

Serial determinations of the ESR, C′ and CRP were performed in sixty-one episodes of myocardial infarction. All three tests became positive in well over 90 per cent of the patients by the third day from onset of the disease. There appears to be no inherent superiority of the newer tests to the well established procedure of the erythrocyte sedimentation rate except for study of the mechanisms of inflammation.

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Seminar on Allergy

The Delayed Type of Allergic Inflammatory Response*

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There has been a renaissance of interest in allergy of the delayed type in the past decade. This widespread interest has generated new experimental observations, which have in turn provoked new ideas. As a result, older concepts concerning this phenomenon have been placed in different perspectives which continue to undergo change. There is increasing awareness of the probability that the mechanism underlying the genesis of delayed allergy has widespread general biologic implications at a cellular level. This is in addition to its role in conditioning altered tissue responses of the host in diseases caused by or associated with specific bacteria.

DEFINITIONS AND GENERAL PRINCIPLES

Allergy of the delayed type is a unique example, and probably the least well understood, of the various types of allergic inflammatory response presumed to be due to an altered immune state. In its typical form delayed allergy is acquired following infection with a wide variety of microorganisms which include bacteria, viruses, fungi and spirochetes. It may also follow contact with plant substances and simple chemical compounds.[1–8]

Delayed allergy plays a prominent role in conditioning the host's response in those bacterial infections characterized by a chronic course and a granulomatous type of inflammatory response. Outstanding examples include tuberculosis, brucellosis, typhoid fever, tularemia, glanders and chancroid. Although the role of delayed allergy appears to be a less prominent factor in conditioning the course of acute infectious disease, it is present in streptococcal,[9] pneumococcal[10] and diphtherial infections.[11] Viral infections which have been shown to induce delayed allergy include vaccinia, lymphogranuloma venereum and mumps. Fungus infections evoking an allergic response of the delayed type include coccidioidomycosis, histoplasmosis and epidermophytosis, as well as sporotrichosis, blastomycosis and aspergillosis. Delayed type allergy is present in syphilis also. Finally, a contact type of delayed allergy may result from exposure to poison ivy, poison oak, sumac, or to a great variety of simple chemical compounds such as arsenic, nickel and mercury.

A primary requisite for the development of bacterial allergy of the delayed type appears to be prolonged focal contact between considerable numbers of intact bacterial cells and the tissues of the host.[12–14] Soluble components of the bacteria have been capable of inducing only the Arthus type of sensitivity.[15]

The development of sensitization usually requires ten days to two weeks following infection or contact—a time consistent with that usually necessary for the formation of antibody to known antigens.

The presence of delayed type allergy is manifest upon testing, usually intradermally, with antigens prepared from the particular causative agent and the inflammatory response is highly specific, i.e., infection with the tubercle bacillus confers sensitivity only to that bacterium or its constituents. The designation of this type of sensitivity as "delayed" stems from the latent period which intervenes between the application of the test antigen and the appearance of the macroscopic manifestations of the inflammatory response. The time lapse in this instance refers

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to the appearance of maximum effects, usually seen at eighteen to twenty-four or forty-eight hours, depending on the degree of sensitivity of the host and the amount of antigen used in the test.

Despite the apparent parallelism with the events which occur in immune responses in general, delayed allergy appears to have no relation to serum antibody, precipitable or otherwise.[16–18] To date, no antibody has been found to mediate or parallel the highly specific inflammatory response to the presence of antigen characterizing the delayed sensitive state.

Moreover, delayed type allergy has not been amenable to passive transfer with serum, in contrast to the consistently successful transfer of this response effected by cells of the leukocyte series.[19–21] Finally, the noxious effects of antigen have been reported to occur without the mediation of blood vessels or smooth muscle, as evidenced by the occurrence of the delayed inflammatory response in the avascular cornea[22] and the recurrent[22–30] if not always consistent[31–33] intimations of a specific cytotoxic effect of antigen upon the explanted cells of the sensitive host in tissue culture.

If we turn now to a consideration of the wheal and erythema, and the Arthus or anaphylactic types of allergic inflammatory response, it will be seen wherein delayed allergy has come to be regarded as unique. The wheal and erythema type of allergy arises spontaneously in man with the clinical syndromes of hay fever and certain types of bronchial asthma. It is classically provoked in sensitive individuals by plant pollens, and its acquisition in man appears to be conditioned by genetic inheritance.

The Arthus or anaphylactic type of response is pre-eminently a man-made sensitivity occurring in both animals and human subjects. It is usually acquired following the parenteral administration of soluble antigens. The original experiment of Arthus was performed in the rabbit; initial injections of antigen intradermally or subcutaneously were without effect but upon repeated injection of antigen the animal became sensitized and responded within a half-hour with a reaction mainly characterized by edema, which persisted several hours. Ultimately, the intensity and duration of the response increased, until necrosis occurred at the injection site.[34]

Chase[1] combines the wheal and erythema and the Arthus or anaphylactic types of allergic inflammation into one broad category designated as the "early responses," chiefly because the macroscopic manifestations of the inflammatory response occur promptly, usually in a matter of minutes. This category however encompasses more than a description of the tempo of events, since both the wheal and erythema and the Arthus responses are characterized by the presence of measurable serum antibody, and each response can be transferred passively by means of serum.[35–38] There are other distinctions which set the early allergic responses apart from the delayed, namely, the antigens which evoke the early response *in vivo* have not been shown to be cytotoxic for explanted tissues of the sensitive host, and the inflammatory response does not occur in the avascular cornea, requiring the presence of blood vessels or smooth muscle to be manifest.[22,39]

The similarities and differences of the early and delayed allergic inflammatory responses are summarized in Table 1. It is of interest that except for more precise knowledge of the chemical constitution of the antigens and of quantitative correlations with serum antibody, cellular transfer and cytotoxicity studies, Table 1 has changed little since Dienes' table of 1932.[40]

In an era conditioned by the development and perfection of quantitative measurements of serum antibody, the absence of measurable antibody has isolated the delayed type of response from conventional immunologic reactions. The lack of correlation with serum antibody continues to impede progress toward an understanding of the delayed response. Thus the distinction between early and delayed types of response has evolved from the chance circumstance of a serologic measurement. This distinction, like Table 1, is man-made and may have a variable relationship to events as they occur in nature. In the discussion to follow it will be seen that the differences between the early and the delayed types of response appear less marked as experimental observations continue to suggest more similarities between them. It becomes increasingly probable that the differences may be variants in degree rather than in kind, as originally postulated by Dienes.[40]

THE NATURE OF THE SENSITIZING PROCESS IN DELAYED ALLERGY

The most consistently reproducible difference between the early and delayed type of allergic response appears to be the presence of measur-

TABLE I

TYPES OF ALLERGIC INFLAMMATORY RESPONSES

	Early Responses		Delayed Responses
	Wheal and Erythema	Arthus or Anaphylactic	
Clinical state	Hay fever, asthma	Serum sickness	Tuberculosis, lymphogranuloma, histoplasmosis, syphilis, poison ivy
Sensitizing material	Pollens	Soluble proteins, carbohydrates	Bacteria, viruses, fungi, spirochetes, plant materials, simple chemicals
Antibody	Present in serum Non-precipitable Heat-labile	Present in serum Precipitable Heat-stable	Absent in serum Absent in cells Unknown
Transfer of sensitivity	With serum	With serum	Not with serum With cells
Cytotoxicity of antigen for explanted sensitive cells	None	None	Present

able serum antibody, and its capacity to transfer sensitivity characteristic of the early response. There is a further distinction within the group of early responses; this is based on the character of the antibody: it is non-precipitable and heat-labile in the wheal and erythema type, and is precipitable and heat-stable in the Arthus or anaphylactic type of response.

If we ask ourselves by what selective and consistent mechanism does the host respond with the production of non-precipitable antibody to one type of antigenic stimulus, precipitable antibody to another type, and as yet no measurable antibody to a third type, the answer is that we do not know. As we lack an exact knowledge of the mechanism involved in the induction and development of delayed allergy, it is difficult to assess the weight of the various factors which may contribute to this process. However, it will be helpful to our understanding of the problem to attempt to analyze the contributions of factors such as the sensitizing agent, the mode of sensitization and the host response.

The Contribution of the Sensitizing Agent. It will be recalled that the intact bacterial cell is required to produce allergy of the delayed type. Whenever attempts have been made to sensitize by means of soluble components of bacteria, the sensitivity achieved has been of the Arthus type.[15] Indeed, the repeated injection of soluble proteins is the classic mode of production of the Arthus type of sensitivity. On the other hand, sensitization with intact bacterial cells may result in the development of both delayed and Arthus type sensitivity. An early and recurrent viewpoint suggests such differences in response may be related to the nature of the antigenic material; e.g., crystalline egg albumin is a relatively pure soluble protein which has a relatively simple chemical structure when compared to the complex mosaic of antigens that go to make up the tubercle bacillus or streptococcus.[8]

Raffel and his colleagues have approached this problem by analyzing the contribution of the various fractions of the tubercle bacillus to the development of delayed allergy. In a series of interesting studies[41–45] they observed that tubercle bacilli extracted with ether, alcohol and chloroform became incapable of inducing delayed sensitivity to tuberculin. However, serum antibodies and anaphylactic sensitivity to the bacillary protein were readily demonstrable. Reconstitution of the chloroform-soluble, wax-like lipid to the bacillary protein restored the capacity to induce tuberculin

sensitivity. If egg albumin was substituted for the protein of the tubercle bacillus and mixed with the wax, delayed sensitivity to egg albumin was produced.[43] Picryl chloride mixed with the isolated wax of the tubercle bacillus and injected parenterally also resulted in the development of allergy of the delayed type to the picryl chloride.[42] The essential component of the waxy substance was found to be a lipopolysaccharide.[44] Choucroun[46,47] has independently reported similar experiments with consonant results. Myrvik and Weiser have subsequently confirmed these observations.[48]

Raffel's interpretation of these data views the tubercle bacillary protein as the specific antigen to which delayed allergy is directed, and the wax is implicated as the non-antigenic material active in directing the host's response to the protein in a delayed fashion. The role of the wax is interpreted as a general biologic one on the basis of similar results achieved when egg white was substituted for the bacillary protein. The observations with picryl chloride indicated to Raffel that there may be a similar lipid substance in the skin which, when combined with picryl chloride, directs the sensitivity achieved along the routes to the delayed response. More recently he has stated that lipoidal factors with similar activity are present in a hemolytic streptococcus of group C and that an analogous substance may be present in vaccinia virus.[45] It is his feeling, therefore, that the delayed allergy of the bacterial, viral or contact type may be the result of the inductive properties of the lipoidal character of the sensitizing material and, when these are lacking, similar lipoids may be supplied by the host. Freund, in a recent review,[49] cites the studies of Landsteiner[50] and Eisen[51,52] indicating the preferential conjugation of simple chemical substances with the proteins of the skin rather than lipoids, as postulated by Raffel.

Raffel suggests further that the directive effect of the lipoidal substances is on some basis other than their capacity to induce cytologic changes of a particular type. In support of this concept similar cytologic changes are provoked by another lipid of the tubercle bacillus—the phosphatide—yet the latter is not capable of inducing delayed allergy to protein materials.[42] In addition, and perhaps of even greater interest, is the observation that egg albumin could be injected into the subcutaneous site of wax deposition two hours after injection of the wax and result in the induction of delayed allergy to the egg albumin. However, if the interval between the injection of wax and subsequent injection of egg albumin was extended to twenty-four hours, delayed allergy did not occur. In a subsequent publication Raffel[45] inclines away from this view and more toward the conditioning effect of the host's cytologic response, as will be indicated later.

The Contribution of the Mode of Sensitization. The route of sensitization appears to condition the type sensitivity which is induced in the host. Swift and Derick[13,14] observed that animals injected subcutaneously with streptococci developed exquisite delayed sensitivity but repeated intravenous injections produced an immune state without sensitivity. Similar findings have been noted for the pneumococcus[53] and the tubercle bacillus.[12] Landsteiner and Chase showed that simple chemical compounds must be applied to the skin in order to produce delayed allergy of the contact type, whereas parenteral injection of the material results in the production of serum antibody and skin reactions of the early type.[54]

Somewhat related to these findings is the response of spontaneously sensitive subjects upon meeting specific pollens in nature. Here the allergic individual responds with the production of non-precipitable, heat-labile antibody. When the pollen is injected parenterally, allergic and non-allergic subjects alike form another type of antibody. This antibody is non-precipitable and differs from the spontaneously occurring antibody in binding antigen, by passing the placental barrier and being heat-stable.[35,55–57] It has been designated "blocking antibody" to describe its capacity to compete with the spontaneously occurring antibody for the neutralization of antigen.

The Contribution of the Tissue Response of the Host. The characteristic tissue response in those bacterial infections in which delayed sensitivity is a prominent feature is of the granulomatous type, as in tuberculosis, brucellosis, typhoid fever and tularemia. An interesting characteristic of these infections is the intracellular residence of the causative microbe.

The cytologic response of the host has been most extensively studied in infections caused by the tubercle bacillus. In response to infection with this microbe the polymorphonuclear leukocyte may predominate early but is soon replaced by the mononuclear cells and round cells.[40,58]

Dienes,[59–62] Hanks,[63] Freund,[64] Chase[1] and Burnet[2] have suggested that the direction induced sensitivity takes depends mainly on the character of the cell population produced by the host in response to the infection. Dienes indicated the importance of the conditioning role of the tuberculous focus in causing protein antigens to incite delayed sensitivity instead of the usual Arthus type. He injected egg white into a tuberculous focus in the guinea pig and induced delayed sensitivity to egg white in addition to anaphylactic sensitivity. He concluded that the unique aspects of tuberculin sensitivity did not reside in the special character of the bacterial antigen mosaic but occurred rather as a result of a special type sensitization. Hanks[63] confirmed and extended Dienes' observations. Freund and McDermott[65] obtained a similar effect by injecting horse serum and killed tubercle bacilli suspended in paraffin oil. In addition the serum antibody response to horse serum was greatly increased in titer and duration. Freund has reviewed these and subsequent observations on the effects of adjuvants on the immune response.[49,64]

In a series of studies on streptococcal hypersensitivity, Swift and Derick[13,14] also concluded that a primary requisite for the development of delayed type of allergy was the production of focal lesions in the tissues of the host.

In a more recent publication, Raffel[45] has also considered that the capacity of the wax to engender the delayed response probably depends on the ability of the wax to convey antigen into cells that are not ordinarily penetrated (e.g., epidermal cells).

In assessing the relative importance of each factor in the induction and development of delayed sensitivity, it becomes apparent that their roles are interdependent and we are examining and describing merely different facets of a similar if not the same property. For example, it would be misleading to attribute to the tubercle bacillary wax alone the crucial role in the production of delayed allergy without considering the route of administration. The effects of both in determining the type of cell population called forth by that specific material in a particular tissue site deserve equal consideration. The situation is somewhat analogous to that encountered in infectious disease, where virulence of an organism or resistance of a host can derive meaning only from the nature of the host's response. Similarly, in allergic states the type of antigen and its route of access to the tissues can derive significance only in terms of the host response. Current interpretations[1,2] favor the nature of the cellular response of the host as the determining factor which influences the direction of the induced sensitive state. This view, however, acknowledges the importance of the nature of the sensitizing agent and its route of access to the host in determining the type of cell population that is evoked.

Chase[66] suggested that the significant events occurring to the antigen, in relation to the cell population ultimately producing delayed sensitivity, take place much earlier in the induction phase than we are accustomed to think. This appears to have the support of Raffel's observation on the failure of wax to induce delayed allergy to egg albumin if the interval between injections is extended from two to twenty-four hours. It might be profitable to define this period more precisely and to correlate the nature of the cell population with the onset of impaired effectiveness of the wax. It would be misleading, however, to expect to find a particular cell type involved in the induction of delayed allergy when there is equal probability that more than one cell type participates in this exceedingly complex biologic response.

THE CONTRIBUTION OF RECENT OBSERVATIONS TO AN UNDERSTANDING OF THE NATURE OF DELAYED ALLERGY

Cellular Transfer. Bail[67] accomplished successful transfer of tuberculin sensitivity in the guinea pig following the intraperitoneal injection of lymph node and splenic cells obtained from sensitive guinea pigs. Fatal systemic tuberculin shock was used as the measure of successful transfer.* Kirchheimer[68] reviewed the early literature describing the variable success achieved with this technic. However, it was not until the contribution of Landsteiner and Chase,[19] and Chase[20,21] that a consistently reproducible technic of cellular transfer became available. Chase's[69] contribution has given impetus to studies related to allergy of the delayed type and to immune responses in general.

Chase[20,21,69] demonstrated that specific cutaneous sensitivity of the delayed type to tuberculin can be transferred to unsensitized guinea

* I would like to thank Dr. Jules Freund for bringing this significant early contribution to my attention.

pigs by the injection of leukocytes isolated from the peritoneal exudates, spleen, lymph nodes or blood of sensitized animals. The intensity of the sensitivity in the recipient varied with the number of cells used and the degree of sensitivity of the donor; its duration appeared to be brief. The cells became inactive after heating at 48°C. for fifteen minutes or upon freezing. This fundamental contribution provides the most direct evidence to date that tuberculin sensitivity is probably mediated by an immune mechanism intimately bound to cells, and is not the result of some non-specific response. Chase's findings were confirmed by Cummings, Hoyt and Gottschall,[70] Kirchheimer and Weiser,[68] Stavitsky[71] and Metaxas.[72] In addition, Kirchheimer, Weiser and Van Liew[73] demonstrated that systemic as well as cutaneous sensitivity to tuberculin was conferred upon recipient animals following cell transfer.

Wesslén[74,75] transferred tuberculin sensitivity using almost pure suspensions of lymphocytes obtained from the thoracic duct of rabbits. Kirchheimer, Hess and Spears[76] have reported that guinea pig peritoneal exudates composed almost exclusively of granulocytes do not transfer tuberculin sensitivity. These findings suggest that the capacity to transfer sensitivity resides chiefly if not exclusively in the lymphocytes and monocytes.[66,69]

Cummings and Hudgins[77] found that cortisone administered to tuberculin-sensitive donor guinea pigs did not inhibit the capacity of cellular transfer. In the recipients of such cells the induced tuberculin reaction was suppressed by cortisone administration; however, the tuberculin reaction became larger upon discontinuing the drug.

Metaxas-Bühler[78] and Carrère and Quatrefages[79] independently demonstrated the transfer of delayed allergy to melitine following cellular transfer with cells from Brucella-sensitive guinea pigs. Although most efforts to transfer sensitivity from one species to another have failed,[66] Kourilsky, Decroix and Ganter[80] reported successful transfer of tuberculin sensitivity from human to guinea pig. Lawrence[81] applied the cell transfer technic to man and reported the successful transfer of tuberculin sensitivity, using intact, viable leukocytes obtained from the peripheral blood. Adopting this model to the streptococcal-sensitive state he was able to transfer delayed sensitivity to intact streptococcal cells, to an extracellular product (streptokinase-streptodornase) and to a streptococcal cellular material (M-substance).[82,83] The observations in man have also been confirmed and extended. Urbach, Sones and Israel[84] transferred tuberculin sensitivity to normal subjects and to patients with Boeck's sarcoid. Recently Good and Varco[85,86] have transferred tuberculin and streptococcal sensitivities to patients with congenital agammaglobulinemia. Porter[87] has transferred tuberculin sensitivity, induced in a patient with congenital agammaglobulinemia following BCG inoculation, to a normal subject by means of cells. Walzer and Glazer transferred the wheal and erythema type of response to pollens in human subjects.[88]

In the studies cited, the leukocytes used have been isolated from the peripheral blood; however, the transfusion of whole blood to tuberculin-negative infants with erythroblastosis fetalis has likewise been shown by Schlange and Hildberg to induce tuberculin sensitivity.

The observations in man following cellular transfer are in general agreement with those made in animals. In man, however, the dosage of leukocytes required for transfer is considerably less than for the animal and the transferred sensitivity persists for several months. It is probable, as Chase has suggested,[66] that these differences represent the relative ease with which man is sensitized to a wide variety of materials.

A further difference has been reported by Lawrence[89] who transferred tuberculin and streptococcal sensitivity in man, using the components of leukocytes disrupted by distilled water lysis or by repeated freezing and thawing. With this finding it became possible to attempt identification of the particular leukocyte component(s) concerned in the transfer of delayed sensitivity. As a working hypothesis, it was assumed that the transfer factor was phagocytized and self-replicated by the cells of the recipient, analogous to the self-replication of viral particles and to the behavior of the DNA of the pneumococcal-transforming principle of Avery, MacLeod and McCarty.[90] To test this assumption, components of leukocytes disrupted by freezing and thawing were treated with desoxyribonuclease and ribonuclease, respectively, before transfer. The results of such treatment did not diminish or abolish the transfer of delayed sensitivity to tuberculin. It was concluded that the transfer factor did not reside in the highly polymerized DNA or RNA components of the donor cell.

In animal experiments the failure to transfer delayed sensitivity or serum antibody by cells damaged by freezing and thawing or by distilled water lysis has been repeatedly and consistently demonstrated.[20,69,91] One exception has been reported by Jeter, Tremaine and Seebohm[92] with the successful transfer of delayed sensitivity to 2,4-dinitrochlorobenzene in the guinea pig, using leukocytes disrupted by sonic vibration. However, this finding could not be extended to tuberculin sensitivity.

It is probable that the results achieved in man following the transfer of delayed sensitivity with disrupted leukocytes is another example of a species difference in relation to this system.

Recently, Pappenheimer and the author[93,94] have confirmed and extended the observations in man, using the diphtheria toxin-antitoxin system. This system offers the advantage that toxin and antitoxin can be detected in minute concentrations by the sensitive rabbit intracutaneous neutralization test. Delayed sensitivity to highly purified diphtheria toxin or toxoid,[11]* and to tuberculin was achieved in non-sensitive, Schick-positive recipients following the injection of frozen and thawed DNase-treated components of leukocytes obtained from specifically sensitive donors.

Antitoxin could not be detected in the cell extracts used to transfer sensitivity and no antitoxin could be detected in the sensitized subject's serum at a time when the transferred sensitivity was maximal. If circulating antitoxin mediates delayed sensitivity to toxoid it must do so in extremely minute concentration or it must differ from ordinary antitoxin in failing to neutralize diphtheria toxin.

Cell-free plasma or saline extracts prepared from intact leukocyte suspensions incubated at 37°C. for one-half hour transfer delayed sensitivity to tuberculin and to diphtheria toxoid. The addition of specific antigen (tuberculin or diphtheria toxoid) to intact leukocytes also results in the transfer of sensitivity by the cell-free supernatant solution. Intact cells treated with toxoid to liberate the transfer factor into the supernatant in this fashion and subsequently frozen and thawed retain the capacity to transfer delayed sensitivity.

Thus far, no specific cytotoxic effect of tuberculin or toxoid on sensitive cells has been clearly demonstrated since untreated control supernatants also transferred sensitivity. The role of relatively minor, non-specific damage to cells in the release of the transfer factor is apparent. In passing it may be noted that elution of the transfer factor into a saline supernatant solution offers the advantage of a less complicated working medium for attempts to identify this factor.

This work[93] has resulted in the formulation of a useful working concept of the mechanism of the delayed reaction based on the data already discussed. The concept views the delayed inflammatory response to a specific antigen as a kind of biologic chain reaction. It is postulated that leukocytes of sensitive individuals contain in their surface structure a type of cellular antibody with a high affinity for antigen. Combination with antigen, possibly mediated by complement, results in the release of the cellular antibody (transfer factor)–antigen complex. The antigen–antibody complex subsequently dissociates and liberates the transfer factor and free antigen. Other sensitive cells may be damaged by combination with dissociated antigen, and non-sensitive cells attracted to the area may engulf the transfer factor, thereby becoming sensitized themselves. In this fashion a progressive process is set in motion which will continue until antigen is exhausted.

The cells of a highly sensitive individual may contain very much larger numbers of transfer-factor particles per cell. Only minute quantities of antigen would be required to liberate many transfer-factor particles, each one of which, following phagocytosis, could render a non-sensitive cell sensitive. Thus, following transfer to the non-sensitive recipient each disrupted cell would in turn serve to sensitize large numbers of the recipients cells. This reaction would not require the presence of serum antibody of the ordinary type. The hypothesis is consistent with the experimental observations and has helped in the design of experiments to test its validity.

Serum Transfer and Transfer with Cell-Free Fluids. There have been scattered reports in the literature concerning the transfer of delayed sensitivity by means of serum. Zinsser and Mueller[95] transferred tuberculin sensitivity in the rabbit by means of serum but discounted the observation because it lacked reproducibility. There have also been reports of the transfer of delayed sensitivity by means of cell-free exudates or supernates or filtrates. McJunkin[96] reported transfer of tuberculin sensitivity by means of

* Toxin and toxoid are indistinguishable by all tests for delayed and immediate sensitivity.[93]

filtrates prepared from peritoneal exudates evoked in tuberculous guinea pigs. Crepea and Cooke[97] reported transfer of delayed sensitivity to poison ivy in the guinea pig following the injection of saline extracts prepared from the spleens of sensitive donors.

Recently Cole and Favour[98] have reported on the transfer of delayed tuberculin sensitivity in the guinea pig by means of a factor present in a subfraction (IV-10) of alpha globulin isolated from the pooled sera of sensitive donors. When fractions II (gamma globulin) and (IV-10) are combined, the transfer of delayed reactivity is inhibited. This is interpreted to explain the inconstant success of Zinsser. Favour suggests that further investigation will be required to determine whether the reaction transferred is a classic tuberculin reaction or of the Arthus type.

Of particular interest, however, is the finding that the donor animals must be skin-tested within forty-eight hours of being bled or transfer does not occur. Favour points out the possibility that lysis of certain host cells by the antigen, *in vivo*, with liberation of antibody into the plasma may occur.

In each of the reports cited (McJunkin, Crepea and Cooke) injection of the sensitive donor with the specific antigenic material seems necessary to obtain the transfer factor free of cells. Our observations[93,94] suggest that the transfer factor is released from human leukocyte suspensions without much cell damage. However, the role of antigen in the release remains uncertain.

Lympholysis. Favour and his associates[99–101] have reported on the *in vitro* lysis of a proportion (20 to 30 per cent) of peripheral blood lymphocytes obtained from the tuberculin-sensitive host in the presence of tuberculin. Washed leukocytes from the tuberculin-sensitive host were found to release into normal plasma a factor which caused lysis of normal leukocytes in the presence of tuberculin. The plasma factor is precipitated with the euglobulins, and is shed into plasma by lymphocytes but not by neutrophilic leukocytes. Wesslén[102] confirmed these observations except that he was unable to demonstrate the plasma factor. Waksman[103] also repeated this work and compared lympholysis with tuberculin skin sensitivity and tuberculin inhibition of fibroblasts and macrophages in tissue cultures obtained from sensitive donors. He found lympholysis did not parallel skin sensitivity whereas tissue culture inhibition did; moreover, the latter response did not require the presence of complement. When lympholysis occurred, it was present only early in the course of sensitization.

The exact significance of lympholysis in relation to the mechanism of tuberculin sensitivity and the transfer of tuberculin sensitivity by means of lymphocytes can only be guessed at. Lympholysis, like tissue culture inhibition, poses the same very difficult technical problems inherent in observing living cells for any extended period when the morphologic response evoked by the test material is a graded one.

More refined biochemical methods have been employed recently to assess this problem. Kerby[104,105] could detect no difference in the release of a lysozyme-like enzyme into the supernatant of human leukocytes from tuberculous and non-tuberculous subjects upon exposure to tuberculin for two hours *in vitro*.

Cruikshank[32] adopted a microspirometric method to study the effect of tuberculin on the oxygen uptake of skin from normal and sensitized guinea pigs. He found that no alteration of the respiratory rate occurred in either.

Chaudhuri and Martin[106] found a depressed succinic dehydrogenase activity in the kidney, liver and spleen of animals infected with BCG. The challenge of sensitized animals with tuberculin resulted in depression of enzyme activity as well.

Pappenheimer and Lawrence[107] have measured the release of lactic dehydrogenase as an index of leukocyte damage. Working with lymphocyte suspensions obtained from a tuberculin-sensitive human they were unable to detect any difference in the quantity or rate of lactic dehydrogenase released in the presence or absence of tuberculin.

Studies on Patients with Agammaglobulinemia. In a series of interesting studies on patients with congenital and acquired agammaglobulinemia Good and Varco[85] have suggested that the inability to produce serum antibody to antigenic materials may be correlated with the failure of plasma cell formation observed in such subjects. They describe the absence of delayed sensitivity in such patients when tested with tuberculin, streptococcal and pneumococcal materials. However, the transfer of delayed sensitivity to tuberculin and to a streptococcal material (streptokinase-streptodornase) was successful in the agammaglobulinemic subject following an injection of leukocytes obtained from the peripheral blood of sensitive donors. Porter,[87]

in a study of a congenital agammaglobulinemic patient, has reported the induction of delayed sensitivity to tuberculin following BCG vaccination and to delayed contact sensitivity to 2,4-dinitrofluorobenzene. Moreover, although the delayed sensitivity to tuberculin was induced, the Choucroun test for tubercle polysaccharide antibody remained negative. Of considerable interest is his observation that the tuberculin sensitivity induced in the agammaglobulinemic subject could be transferred to a normal subject by means of leukocytes isolated from the peripheral blood of the former. These results suggest that the mechanism underlying the induction or transfer of delayed sensitivity can function effectively in the absence of the capacity to form serum antibody. It would also seem that the presence of plasma cells is not required.

Such a dichotomy may be interpreted to mean either that the histologic population related to production of delayed sensitivity is independent of that related to the production of serum antibody, or that a maturation arrest has occurred in the stem cell which usually responds to antigenic stimuli by becoming a plasma cell.

Early and Delayed Reactions to Serum Antigens and Their Study with Cellular Transfer. Isolated observations made by Dienes and Simon,[108] Simon and Rackeman,[109] and Mote and Jones[110] have called attention to the capacity of animals and man to develop delayed sensitivity to soluble antigens (guinea pig and rabbit sera) during the course of repeated skin-testing with these materials. If the testing is continued, the delayed sensitivity is subsequently supplanted by urticarial responses. These apparent exceptions to the usual behavior of soluble proteins, bacterial or other, producing only the Arthus type of sensitivity and serum antibody[15] have been studied again with interesting results.

Gell and Hinde[111] and Metaxas[112] abroad, and Tremaine and Jeter[113] in this country have independently conducted experiments which confirm these observations. Gell and Hinde[111] immunized rabbits with human plasma or ovalbumin and correlated histologic studies of Arthus and intradermal reactions and serum antibody in the donors and recipients of serum and cell transfer. They conclude that the Arthus reaction is a biphasic one. In the beginning of the course of sensitization it consists of the delayed type of sensitivity characterized by mononuclear cells and no serum antibody. Later in the course of sensitization the maturation of mononuclear cells to plasma cells occurs coincident with the production of serum antibody. The dissociation of the two components is also seen following transfer studies. Recipients of cells showed a weak immediate type of reaction and a greater delayed mononuclear reaction. No plasma cells were observed in either group of recipients.

The authors suggest that in the beginning of the immunization procedure the reaction of all of the cells of the reticuloendothelial system to specific antigen is altered, resulting in the delayed type of response. The production of serum antibody and the Arthus type of response follows upon subsequent maturation to plasma cells. However, one cannot conclude from studies of this kind that the delayed response necessarily precedes the production of serum antibody. Conclusions based on the time of appearance of skin sensitivity as opposed to the time of appearance of serum antibody are not justified, since there may be a great difference in the relative sensitivities of the methods of testing.

In relation to the plasma cell, observations of this type are consonant with the findings of Coons[114,115] and Good and Varco.[85]

DELAYED ALLERGY OF THE CONTACT TYPE

It was noted previously that sensitization of the delayed type could follow exposure to diverse plant and chemical compounds. The qualification of delayed allergy of this type as "contact" refers to the usual mode of sensitization and elicitation. The sensitizing materials are usually of low molecular weight (haptenes) and by themselves are not antigens. Through the proposal of Wolff-Eisner and the experimental corroboration of Landsteiner and Jacobs,[116,117] it appears that simple chemical compounds function as conjugated antigens after combination with tissue protein *in vivo*. Direct experimental evidence that this is actually the case has only recently been secured by Eisen and his colleagues.[51,52,118] Low molecular substances active in eliciting delayed reactions were demonstrated to combine with protein of the skin *in vivo* and *in vitro*.

Induction of the delayed sensitive state follows repeated application of the inciting material to the skin. Following a latent period of five to twenty days[1] sensitivity becomes manifest as a delayed erythematous and vesicular skin reaction to the patch test. The sensitivity cannot be transferred by means of serum and there is no

correlation between serum antibody and the occurrence or degree of delayed sensitivity. In the guinea pig the sensitivity has been transferred by means of cells of the leukocyte series.[19,92,119]

It will be recalled that parenteral injection of a haptene of the type under discussion, picryl chloride, results in the formation of serum antibody and the immediate allergic response. However, delayed sensitivity of the type induced by repeated application of picryl chloride to the skin can also be achieved following intraperitoneal injection of mixtures of this substance and killed tubercle bacilli[64] or the isolated wax fraction of tubercle bacilli.[42]

In addition the two types of response, immediate and delayed, may appear in the same subject simultaneously as has been noted following bacterial sensitization. However, the particular sensitivity resulting from exposure to simple chemicals is determined mainly by the chemical nature of the sensitizing substance. Some chemicals evoke almost exclusively delayed responses, some mainly immediate responses and some combinations of the two.[1]

Chase[120,121] has shown for picryl chloride that the same cells used to transfer delayed sensitivity can also produce anaphylactic sensitivity and serum antibody in the recipient. He has also extended this observation to show that cells secured from donors stimulated with such antigens as diphtheria toxoid can transfer serum antibody[122]—an indication that delayed sensitivity to the antigen is not a requirement for the capacity of the cells to transfer serum antibody. If the cells are non-viable, transfer of delayed sensitivity or serum antibody does not occur. Chase[123,124] fed sensitizing substances to non-sensitized animals and thereby induced resistance to subsequent sensitization of the immediate or delayed type to the substance fed. However, such animals were capable of acquiring sensitivity to the substance following cellular transfer.

From such experimental results Chase[1] concludes that the mechanism underlying sensitization of the contact type is intimately related to the antibody-producing system. Although the exact mechanism remains unknown, he has shown that the type of sensitivity produced depends upon the mode of sensitization of the donor. He also suggests that prolonged duration of the induced sensitive state following cell transfer may be due to a secondary phase of active sensitization.[125] Chase's observations have been confirmed and extended by Harris and his colleagues employing the cellular transfer system to study a variety of transferred serum antibody responses.[91,126]

There have been various isolated reports of successful transfer of contact allergy of the delayed type by means of cell-free materials. Ballestero and Mom[127] transferred contact sensitivity in man, using blister fluids prepared by the Urbach-Koenigstein technic. Crepea and Cooke[97] similarly transferred contact sensitivity in the guinea pig, using extracts of splenic cells.

The reports have received recent experimental support from the results of Jeter, Tremaine and Seebohm[92] who were able to transfer delayed sensitivity to 2,4-dinitrochlorobenzene in the guinea pig by means of cell extracts prepared by sonic vibration. The authors interpret the failure to transfer tuberculin sensitivity as a probable reflection of the degree of sensitivity achieved in donor animals. The variation in species and the degree of sensitivity achieved to specific materials within the species could explain these findings.

Scattered attempts to transfer contact allergy of the delayed type in the human subject by means of cells have not as yet been as consistently successful as the transfer of bacterial sensitivity.[128]

Baer and Sulzberger,[129] and Baer, Serri and Kirman[130] have attempted to transfer delayed sensitivity of the contact type in man, using cells obtained from the peripheral blood. Only a few recipients in each series became sensitive. Because of the prolonged duration of the induced sensitive state, the authors attributed the success of the transfer to antigen carried over by the cells.

GENERAL BIOLOGIC IMPLICATIONS OF DELAYED ALLERGY

There is a considerable body of experimental evidence to suggest that the mechanism of delayed allergy is in some way involved in the genesis of such apparently diverse phenomena as the rejection of homografts and transplanted tumors, certain types of encephalomyelitis, neuritis or uveitis, aspermatogenesis and the Shwartzman reaction.

The Rejection of Normal and Abnormal Tissues. The thought that the host's rejection of skin homografts is mediated by the acquisition of delayed allergy to genetically unrelated tissue received experimental support from Medawar's observations.[131–134] The analogy to allergy of the delayed type is based on the following findings. Initial skin grafts applied to recipient animals

are rejected in about ten days; a second graft from the same donor is rejected in an accelerated fashion (four to six days). The quantity of skin used to sensitize the recipient conditions the tempo and intensity of the rejection. A skin graft from another donor does not undergo accelerated rejection when applied to this same recipient.

Medawar[135] applied tissue culture and transfer technics to this problem. He was unable to demonstrate accelerated rejection of homografts following transfer with serum from sensitized animals. In addition, tissue culture explants of donor skin were not effected by the presence of sera, cells or cell extracts obtained from animals sensitized to donor's skin. However, leukocytes obtained from the donor conferred on non-sensitive recipients the capacity to react to an initial graft from that donor in an accelerated fashion. This could not be accomplished when the leukocytes were injected intravenously, only following intradermal injection. Billingham and Sparrow have recently confirmed and extended the observations using homologous, dissociated. viable epidermal cells to accomplish transfer of this sensitivity in rabbits.[136]

Experimental evidence supporting this concept has resulted from extension of this work by Medawar and his associates.[137,138] They observed that the *in utero* injection of strain A mice with blood or tissue mash from strain B conferred on litters of strain A the ability to tolerate skin grafts from strain B mice indefinitely. However, following the injection of lymphoid tissue from normal Strain A mice into such tolerant mice the skin graft was rejected in the usual manner.

In this connection it will be of interest to reconsider the studies of Good and Varco[139–141] on agammaglobulinemic patients. In addition to the studies described earlier, they reported the survival of a skin homograft in such a patient for at least eleven months. Interpreted in the light of absence of bacterial allergy in these individuals, the survival of foreign skin was consonant with an impoverished capacity to develop delayed sensitivity. However, the more recent and direct evidence of Porter,[87] referred to earlier, would indicate that the agammaglobulinemic patient studied by him could and did develop delayed allergy to tuberculin and to 2,4-dinitrofluorobenzene. Realizing that one cannot generalize from each study[85,87,139] made in a syndrome which has still to be fully defined, such observations remain provocative, particularly in relation to the development of delayed sensitivity in the face of homograft tolerance. It may be inferred that the mechanism underlying the development of homograft rejection appears to require the presence of serum antibody of some type in addition to the capacity to develop delayed sensitivity.

Transplanted tumors evoke, in general, the same type of response as normal tissues. The same type of analogies can also be inferred in relation to the mechanism of rejection and delayed allergic responses.[142–144]

Mitchison transferred specific tumor tissue sensitivity to normal mice by means of an intraperitoneal injection of lymph node cells obtained from sensitized mice.[145–147]

Analogous results using a different technic have been obtained by Algire and his colleagues.[148–151] It was shown that transplanted normal or tumor tissues could survive indefinitely in diffusion chambers impermeable to the recipient's leukocytes and macrophages. This occurred in the presence of free interchange of the recipient's extracellular fluids. Destruction of the transplanted tissues occurred if the diffusion chamber was permeable to the recipient's leukocytes or if washed splenic cells from specifically sensitized mice were added to the cell-impermeable chamber.

The Development of Isoallergic Encephalomyelitis and Neuritis. Disseminated encephalomyelitis occurs as a complication coincident with or following infection caused by a number of viruses. Rarely it may occur following inoculation with rabies vaccine and smallpox vaccine.[152] The demonstration of a similar entity produced in monkeys, following the injection of autolyzed brain suspensions, stimulated interest in this field.[153]

Kabat, Wolf and Bezer,[154] and Morgan[155] independently and at the same time reported that the addition of adjuvants, according to Freund's technic, to suspensions of brain tissue increased the ease of induction and shortened the latent period for the development of encephalomyelitis in the monkey. It was found that this entity could be produced in the guinea pig as well by Freund and his colleagues,[156] in the rabbit by Morrison,[157] in mice by Olitsky,[158] and in the dog by Thomas and his associates.[159]

Evidence that encephalomyelitis represents a delayed type of allergic response is inferred from its lack of correlation with serum antibody, in the failure to transfer it with serum, and in the

tuberculin-like skin tests to brain tissues evoked in treated animals.[154a]

Lipton and Freund[160,161] have recently transferred experimental allergic encephalomyelitis in the rat by means of parabiosis. The consistent failures to transfer with serum favors the interpretation that the results obtained are related to the cross circulation of leukocytes. However, in a recent review Freund[49] points out that it has not been shown which of the elements of the blood is responsible for the transfer.

Freund, Stern and Pisani[156] evoked both encephalomyelitis and skin sensitivity to suspension of rabbit brain or spinal cord in the guinea pig. The skin reaction was of the delayed type and has been transferred passively with lymphoid cells but not with serum.[162]

Experimental allergic neuritis[163] and allergic uveitis[164] are now being explored by the use of similar technics.[49]

Aspermatogenesis. Freund and his colleagues[49, 165–167] have described the development of aspermatogenesis in the guinea pig following a single intracutaneous injection of homologous testicular material combined with adjuvant. The process is species- and organ-specific and cannot be transferred by means of serum or cells.

The testicular antigen evokes systemic and skin sensitization. Freund[49] suggests that this is not directly related to aspermatogenesis since the latter response requires mycobacteria to be present at the site of injection of antigen.

The Shwartzman Phenomenon. The recent reappraisal of the Shwartzman phenomenon by Thomas and his colleagues[168] would suggest that this reaction, despite its apparent lack of specificity, may be a manifestation of an immune response. Stetson[169] has recently documented the similarities between this response and certain reactions incident to bacterial allergy of the delayed type.

THE RELATIONSHIP OF DELAYED ALLERGY TO DISEASE STATES IN MAN

If we consider the basic principles of the delayed allergic response in relation to our understanding of human disease, there are two broad categories of disease to which this information is applicable. In the one instance there is a group of infectious diseases for which the conditioning role of delayed allergy has been demonstrated. The other category is composed of a group of diseases associated with infectious processes in which the contribution of delayed allergy to the disease process is suspected but not proved.[170,171]

Diseases in Which the Role of Delayed Allergy Has Been Demonstrated. Of the infectious diseases, tuberculosis is an outstanding example of the effect of delayed allergy on the response of the host to the infectious process. The relationship of induced allergy to the pathogenesis of the disease and the type of lesion produced by the tubercle bacillus is reflected in the events incident to the Koch phenomenon. In essence, Koch demonstrated that the guinea pig does not react to the local injection of tubercle bacilli until two to three weeks have elapsed. At this time, coincident with the development of delayed allergy, there is a focal reaction around the injection site. Subsequent injections of tubercle bacilli also evoke a delayed inflammatory response which tends to inhibit dissemination of the bacilli.[7]

The parallel situation in human infections is the acquisition of the "Ghon complex" as a result of the first meeting with tubercle bacilli as compared to the caseating, necrotizing type of inflammatory response in the lung which occurs in the adult reinfection type of tuberculosis. Although other factors are operative (virulence of organisms, nature of pulmonary tissue, resistance and the like), it would appear that the caseation necrosis and subsequent excavation are examples of Koch phenomena occurring in the lung. With excavation and aspiration of the cavity and its contents many other foci of Koch phenomena may be disseminated throughout the lung.[4,5,172] It is of interest to recall that although this effect has been shown to be produced by living or dead tubercle bacilli, most bacilli in human infections are alive and in addition are producing tuberculin in this favorable milieu.

The concept of a direct relationship between tuberculin allergy and production of symptoms in this disease has been reinforced by the consistent results of many planned and occasional inadvertent experiments. Systemic symptoms evoked by relatively small amounts of tuberculin are seen following the diagnostic skin test performed on sensitive subjects. Larger amounts of tuberculin inhaled by laboratory workers preparing this material have caused more serious symptoms. There is also the recorded observation of flaring up of quiescent lung lesions following the administration of large amounts of tuberculin.[4,5]

The caseation necrosis of adult tuberculosis, in addition to favoring a protracted course and impeding spontaneous eradication of the bacillus, probably also inhibits the effectiveness of antimicrobial therapy in this disease. MacLeod[173] has suggested that the development of resistance to antimicrobial therapy is favored by the impediment to diffusion of the drug which the tuberculous lesion presents. This is conducive to the growth of strains of tubercle bacilli exposed to low concentrations of the drug within the lesion—an excellent means of selecting resistant strains.

Although tuberculosis and tuberculin allergy are extreme examples of bacterial allergy, similar factors may be operative in conditioning the manifestations to other bacterial and fungous infections. An example of this latter group is brucellosis. All of the protean symptoms of this disease can be produced in infected individuals following the injection of brucella extracts.[174]

Diseases in Which the Role of Delayed Allergy Is Suspected but Not Proved. Since the exact cause of rheumatic fever is unknown, many theories have been proposed to explain its etiology and pathogenesis. This topic has been the subject of excellent reviews by Swift[175,176] and more recently by Fischel[177] and by Waksman.[178] With the cumulative evidence linking most cases of rheumatic fever with a preceding hemolytic streptococcal infection, current interpretations favor the view that this disease develops as a delayed complication of streptococcal infection.[179,180] This viewpoint is predicated upon an impressive body of clinical and experimental data. In addition, it has served to clarify the possible theoretic and experimental approaches to the problem of how rheumatic fever may develop. The answer to this problem may lie in the biologic characteristics of the hemolytic streptococcus[181] or in a peculiarity of the host's response to infection with this organism.[180]

Of the forty-odd types of streptococci which comprise group A, an infection with any type may precede the development of rheumatic fever and infection with any other type may cause a recurrence of this disease. This experience would suggest that the rheumatic state develops in relation to some property common to streptococci of group A as a whole, rather than in relation to a property of any specific type within the group. In addition the low, overall incidence of rheumatic fever (3 per cent) in an epidemic of streptococcal infections suggests a peculiarity on the part of the specific host in response to infection with this organism. That this selective relationship of the host response is directed specifically to the hemolytic streptococcus is demonstrated by the abrupt fall in the incidence of rheumatic fever when the epidemic is interrupted with penicillin therapy.[182,183]

The prevailing concept is that the peculiarity of the host response which results in rheumatic disease is based on an allergic mechanism. Interpretations concerning the type of allergic response which may mediate the development of rheumatic disease have fluctuated between the Arthus type with horse serum sickness as its model and delayed bacterial allergy with tuberculin hypersensitivity as its model. This topic has recently been reviewed comprehensively by Fischel.[177]

The original basis for considering rheumatic fever an analogue of horse serum sickness hinged mainly on the presence of polyarthritis in each disease.[184] This interpretation was bolstered when the lesions of periarteritis nodosa were found by Rich in patients who had horse serum or sulfonamide serum sickness. It received experimental support following the demonstration of similar lesions induced in animals following the injection of foreign protein. Rich subsequently included periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis as examples of diseases probably resulting from focal anaphylactic reactions of the Arthus type of immune mechanism.[185]

The clinical and pathologic similarities of this group of diseases and serum sickness have been well documented. In the human disease, however, there has been no demonstration of an immunologic similarity. The well defined temporal relationship between the appearance of precipitating antibody to the proteins of horse serum and the development of clinical serum sickness[186] has not been found in serum sickness states evoked by haptenes like the sulfonamides or penicillin, nor has it been found in rheumatic fever. In rheumatic fever serum antibodies to streptococcal antigens have been studied but no direct relationship has been found between the antibody pattern and the presence, severity or activity of the disease.[177] In general, however, patients in whom rheumatic

fever develops following streptococcal infections have a greater antibody response than patients with uncomplicated infections.[187]

When this problem is assessed with the streptococcus or its products as the test material in experimental animals or man, the accumulated data fulfill the criteria for the delayed type of allergic response as the mechanism which mediates the streptococcal hypersensitive state.[83] The criteria fulfilled include the requisite for the intact bacterial cell to induce the sensitive state;[9,13,14] the delayed skin sensitivity to streptococcal materials *in vivo*,[188,189] and the cytotoxic effect of streptococcal antigens on explanted cells of the sensitive host *in vitro;*[26] the lack of correlation between serum antibody and the state of tissue sensitivity;[18] failure to transfer such sensitivity with serum[188] and successful transfer with cells of the leukocyte series.[82] Whether the delayed hypersensitivity to streptococcal antigens occurring following streptococcal infection in man in any way reflects the altered tissue responses to this microbe which characterizes rheumatic fever has not been demonstrated.

Thus, interpretations of the allergic mechanism postulated for the pathogenesis of rheumatic fever vacillate between the Arthus type and the delayed type of response. The two views need not be mutually exclusive since it becomes increasingly probable that the two types of allergic response may represent variations of the same immunologic mechanism. That this may indeed be the case is supported by the experimental evidence of Gell and Hinde cited earlier.[111] It will be recalled that these authors presented data to indicate that a delayed allergic response to protein antigens may occur as an initial and an incomplete phase of Arthus sensitivity.

SUMMARY

The delayed type of inflammatory response is the most common allergic response encountered in human disease states. It occurs extensively in man as a result of natural infections with bacteria. It does not affect only the genetically susceptible few.

Although it is a highly specific altered immune response, the antigen which induces delayed allergy and the antibody which mediates it have not been detected. It differs from early allergic responses which are associated with a measurable serum antibody and are transferred by such sera.

The induction of delayed allergy, the manifestations of its noxious effects and the capacity to transfer the response are intimately bound to the cells of the sensitive host. To date delayed allergic responses have been transferred only with cells of the leukocyte series or extracts prepared from cells. Conventional antibody has not been detected in the cell extracts which transfer this response, or in the recipients of such extracts at a time when delayed allergy is present. The exact mechanism by which minute amounts of cell fragments cause the human recipient to respond to specific test materials in the manner the donor responded to the specific bacterial infection is not known. The chemical nature of the transfer factor liberated from cells also is not known.

Delayed allergy can be induced in and transferred from congenital agammaglobulinemic patients by means of cells in the absence of the capacity to produce serum antibody. A reevaluation of early and delayed reactions to serum antigens suggest that delayed allergy may be an initial and incomplete phase of the Arthus response.

Investigations concerning the mechanism of delayed allergy of the contact type suggest that the type of response induced by sensitization depends upon the chemical structure of the sensitizing agent. Moreover, the type of response achieved following cellular transfer in turn depends upon the mode of sensitization of the donor animal. Although the mechanism by which this occurs is unknown, it is thought to be in the nature of an antibody response.

In addition to its immunologic applications, the mechanism of delayed allergy has extensive biologic ramifications at a cellular level. It appears to be operative in such diverse phenomena as skin homograft rejection, tumor transplant rejection, encephalomyelitis, neuritis and uveitis, aspermatogenesis and the Shwartzman reaction.

Finally, the relation of the delayed allergic inflammatory response to the pathogenesis, symptomatology and course of infectious disease is discussed, with tuberculosis as an example of the clinical application of this basic immunologic concept. That a similar conditioning to hemolytic streptococcal infections may result in rheumatic fever is considered to be probable but as yet is unproved.

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Combined Staff Clinic

Disorders of Renal Tubular Function

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The Clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. GILBERT H. MUDGE: The kidney has at least three general functions: first, it is an active organ of metabolism carrying on many biochemical reactions not dissimilar to those of the liver; second, with a blood flow of about one-fifth of the cardiac output the kidney serves an important regulatory function for the general circulation; and third, it is an organ of excretion, and by the formation of urine serves to control the volume and composition of body fluids. In this Conference we are going to discuss in particular abnormalities related to the last function, namely, the excretion of urine.

Our general thesis will be that just as there are many separate mechanisms which determine normal tubular function, by the same token there are many types or patterns of dysfunction. There is, therefore, not just a single type of renal insufficiency. We shall try to emphasize the nature of some of these specific disturbances, the common ones and, for the sake of illustration, some quite rare ones.

As you all know, modern technics permit the measurement of three types of renal function which determine the composition of the final urine. These are glomerular filtration, tubular reabsorption and tubular secretion. We will pay relatively little attention to variations in the filtration rate but will focus our attention on the reabsorptive and secretory capacities of the tubule. The first topic will deal with abnormalities in glucose reabsorption and this will be presented by Dr. Taggart.

DR. JOHN V. TAGGART: The normal mechanism for the tubular reabsorption of glucose operates with remarkable efficiency. Of the approximately 180 gm. of glucose filtered daily through the glomeruli of an average adult only trace amounts escape into the voided urine. Direct puncture studies in the mammalian kidney have shown that the concentration of glucose in the glomerular filtrate is identical with that in the plasma. As the filtrate proceeds down the tubule a major portion of the filtered electrolyte and water is reabsorbed in the proximal convoluted segment. It is worth emphasizing that glucose reabsorption outstrips even this process, for the tubular urine is almost sugar-free by the time it reaches the midpoint of the proximal convolution.[1] Thus we can place all the major events in the disposition of glucose by the kidney high in the nephron.

The load of glucose presented to the tubules for reabsorption can be increased by progressive elevation of the plasma level. If this is done, small amounts of glucose begin to appear in the urine when the plasma level has reached 160 to 200 mg. per cent, which consequently represents the minimal renal threshold for glucose. However, the quantity of glucose reabsorbed continues to increase as the plasma level rises, and keeps pace fairly well with the filtered load up to a critical point. Eventually the quantity of glucose being reabsorbed reaches a maximal rate, indicating saturation of the transport system, and any additional glucose presented to the tubule escapes into the voided urine. This maximal rate (Tm_G) is approximately 350 mg. glucose per minute in the normal human adult.[2]

There is a feature of glucose reabsorption in renal disease which merits comment. It is surprising that the progressive and extensive alterations of renal architecture induced by diseases, such as glomerulonephritis and pyelonephritis, so rarely result in glycosuria. That glycosuria is an unusual occurrence in these circumstances is attributable in part to the fact that the pathologic process so rarely singles out only the glomeruli or tubules for destruction. In the early phase of diffuse glomerulonephritis, when glomerular damage outstrips tubular damage, no problem with respect to glucose reab-

sorption is posed. In the early phase of pyelonephritis we may well be dealing with a predominantly tubular lesion but the damage is probably limited more or less to the distal portions of the nephron. While both glomerular and tubular damage may be extensive in the later phases of glomerulonephritis or pyelonephritis, the compromised tubules are usually still capable of dealing with the ever diminishing filtered loads of glucose.

There are clinical situations, however, in which glycosuria is the direct result of renal damage. This may be the case occasionally in the early recovery phase following the acute toxic nephrosis due to mercury, uranium salts or cyanide, or following any episode of acute urinary suppression associated with tubular necrosis. In the early diuretic phase glomerular filtration is at least partially restored in advance of tubular regeneration. Consequently, the volume of urine may be large and its composition may be that of an unmodified, or only partially modified, glomerular filtrate. The glycosuria in such cases is usually transitory and regresses and disappears as tubular regeneration proceeds to restore a more normal balance between glomerular and tubular activity.

Let us turn our attention now to those conditions, more permanent in nature, which may be classified as renal glycosuria. One of these is the Fanconi syndrome, a condition in which glycosuria is accompanied by other renal tubular defects. Since the speaker to follow, Dr. Bradley, will deal with this in detail, I shall say no more about it. I should like to discuss what has been called by some "true renal diabetes"—its incidence, diagnosis and, more particularly, a consideration of the possible mechanisms underlying its occurrence.

The term "true renal diabetes" may be said to apply when the following circumstances are encountered: (1) when appreciable quantities of glucose are present in all urine specimens, whether collected in the fasting state or postprandially, (2) when the fasting blood glucose is within normal limits and there is a normal glucose tolerance, and (3) when moderate doses of insulin have little or no effect on the glycosuria. In addition, Marble has pointed out that the quantity of glucose in the urine is more or less independent of the diet. Rigid adherence to these criteria may exclude a limited number of individuals whose minimal renal thresholds for glucose are only slightly lower than normal, for example, 130 mg. per cent, and who should be considered to have renal glycosuria. However, by adhering to these criteria one will safely exclude the alimentary glycosurias and the occasional patient with mild diabetes who has a normal fasting blood sugar but whose morning urine specimens may contain traces of glucose from the preceding day.

The incidence of true renal glycosuria must be very low. Of some 22,000 cases of melituria collected at the Mayo Clinic and in Montreal, only two or three per thousand appeared to have true renal glycosuria. The disorder may occur at any age but frequently is detected very early in life. In some of the cases there is a clear-cut family history. There should be no evidence of progressive renal disease; the persons who have been followed for many years appeared to be no worse off at the end of that time than when the disorder was first detected.

The renal defect common to all cases of renal glycosuria is a low renal threshold for glucose. One can conceive of at least two mechanisms which might account for this disorder. In thinking of renal mechanisms, it is worth recalling that the kidney is not one gigantic nephron, for the kidneys actually contain some two million nephrons each elaborating urine more or less independently of the others. The first theoretic situation to be considered is one in which there is a homogeneous population of defective nephrons. Each of the defective nephrons, while capable of reabsorbing the bulk of glucose presented to it by filtration, fails to reabsorb a certain fraction. If such were the case, one might expect to find some depression of the glucose Tm, the degree of depression depending upon the degree of glycosuria. The second theoretic situation is one in which there is a heterogeneous nephron population. It is reasonable to assume that the filtering capacities of the individual glomeruli vary somewhat within any given kidney and that the lengths or reabsorptive capacities of the proximal tubular segments vary in a similar manner. It would be a very provident Nature that always attached the larger glomeruli to the longer tubules, the medium-sized glomeruli to medium-sized tubules and so forth. It is conceivable that an unusual degree of heterogeneity would yield some nephrons with relatively large glomeruli attached to small proximal tubules—a situation in which tubular reabsorptive capacity might be exceeded even at normal plasma levels of glucose. At the other end of the

distribution curve one ought to find nephrons of the opposite constitution, that is with small glomeruli and long tubules. In the latter group of nephrons the plasma level of glucose would have to be raised to unusually high values to achieve saturation of the glucose-transporting mechanism. Even with such a degree of heterogeneity, however, it is quite possible that the glucose Tm for the total nephron population might be normal.

TABLE I
RENAL FUNCTIONS IN RENAL GLYCOSURIA*

Glomerular Filtration Rate (Normal = 130 ± 15 ml./min.)		Glucose Tm (Normal = 350 ± 50 mg./min.)	
Range (ml./min).	No.	Range (mg./min.)	No.
86–100	3	51–100	1
101–115	5	101–150	4
116–130	4	151–200	3
131–145	4	201–250	4
146–160	1	251–300	3
		301–350	2
Total	17	Total	17

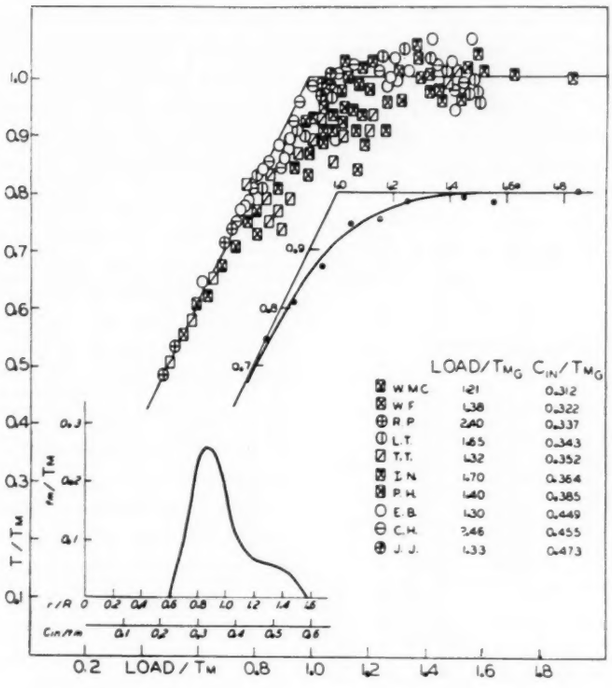
* Data assembled from series of Reubi,[3] Lambert[4] and Bradley et al.[5]

Only a limited number of cases of well documented renal glycosuria have been studied by adequate clearance technics. From a quick review of the available literature I have gathered together data from seventeen patients, nine examined by Reubi[3] in Berne, three by Lambert[4] in Brussels and five by Bradley et al.[5] of this department. In these seventeen individuals the glomerular filtration rates ranged from 84 to 152 cc. per minute, as shown in Table 1. Accepting the approximate normal value as 130 ± 15 (S.D.) cc. per minute, we find that fourteen of the seventeen had filtration rates falling within ±2 standard deviations of the normal mean. It would appear safe to generalize that the filtration rate in renal glycosuria is normal or minimally depressed. Effective renal plasma flows, estimated in several of the patients, were close to normal.

The values obtained for glucose Tm present a very different picture. If the normal Tm is accepted as 350 ± 50 mg. glucose per minute, only five of the seventeen values fell within two standard deviations below the normal mean, while the remaining twelve ranged from 93 to 220 mg. per minute. It is of interest to note that the cases do not appear to subdivide themselves into two or more distinct categories but are fairly evenly distributed from the lowest to the highest values. Nor is there any apparent relationship between the familial type of renal glycosuria and the magnitude of the glucose Tm. The excretory Tm for p-aminohippurate was essentially normal, even in the face of a markedly depressed glucose Tm. Thus the two transport mechanisms, both presumably located in the proximal convolution, may be markedly abnormal and normal, respectively, in the same individual.

A second experimental approach to the appraisal of heterogeneity in the nephron population is by the glucose titration method of Smith.[6] In such experiments the quantity of glucose transported (T) per unit of time is related to the load (L) presented over a wide range of plasma glucose concentrations. The usual relationship is depicted in Figure 1A, which presents the data obtained by Smith and his associates[2] in ten normal subjects. It is evident that reabsorption (T) approximates the filtered load (L) very nearly to the point of saturation (Tm). The small insets in the lower portions of Fig. 1 present calculated frequency distribution curves relating the relative glomerular activity (r/R) and glucose reabsorption (tm/Tm) (cf. Smith[6] for precise definition of terms and methods of calculation). Stated simply, it may be said that the data are consistent with a fairly homogeneous population of nephrons in the normal kidney. Comparable data from three individuals with renal glycosuria and only slightly depressed glucose Tm (253 to 304 mg. per minute) have been obtained by Reubi[3] and are presented in Figure 1B. While I am certain that Dr. Reubi does not attach great significance to the exact configuration of his calculated frequency distribution curves, his data suggest the existence of two categories of anatomically or functionally dissimilar nephrons. In contrast, three individuals with renal glycosuria and low Tm yielded unimodal frequency distribution curves.

In summary, it appears probable that no single explanation will adequately account for all the cases which are grouped together as "true renal diabetes." In some there is very suggestive evidence for an anatomic or functional heterogeneity of the nephron population while in



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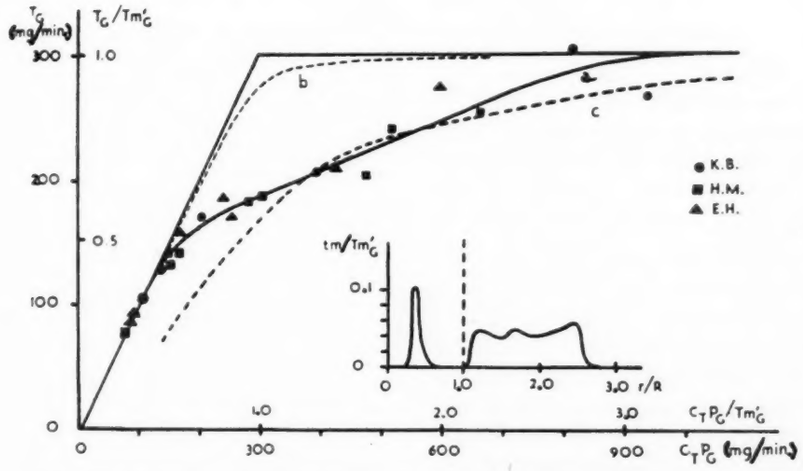

1B

FIG. 1A and B. Glucose titration curves in ten normal human subjects (A) and in three patients with renal glycosuria (B). Symbols represent individual collection periods relating glucose reabsorption (T or T_G) to filtered load of glucose. The small insets are the calculated frequency distribution curves describing the nephron population. (Figure 1A from Smith, H. W.,[2] courtesy of Oxford University Press; Figure 1B from Reubi, F. C.,[3] courtesy of Little, Brown and Co.)

others there is equally convincing evidence that one may be dealing with a homogeneous population of defective nephrons.

DR. MUDGE: Let us turn now to problems of salt and water transport by the tubule. We shall review very briefly some mechanisms of electrolyte transport and then try to give examples of clinical abnormalities. We shall limit our discussion to sodium, potassium, bicarbonate and chloride.

In Figure 2 I have attempted to summarize in schematic fashion some tubular functions relating to electrolyte transport. The first reaction is the reabsorption of sodium with a fixed anion, usually chloride. Although this is depicted as occurring in the proximal tubule,

there is no reason to believe that it does not occur more distally as well. The second reaction is the reabsorption of potassium, presumably by the proximal tubule. The third reaction is the secretion of potassium in exchange for sodium. This is believed to occur in the distal tubule.

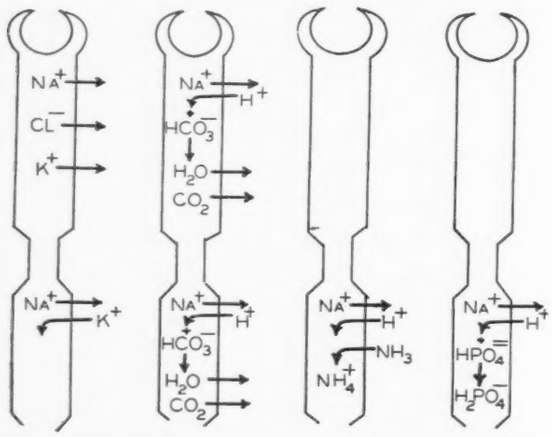

FIG. 2. Schematic diagram of electrolyte reabsorption by renal tubule. (From Ion Transport across Membranes, edited by Clarke, H. T., courtesy of Academic Press, Inc.)

Inasmuch as potassium is both reabsorbed and secreted by the tubule, it is impossible to estimate the magnitude of each process with absolute certainty. However, the simplest interpretation of all the data that have been accumulated to date is that the filtered potassium is for the most part r absorbed, and that the potassium which appears in the voided urine is secreted by the tubule. The "proof" for this—and the word "proof" is in quotation marks—is that in at least ten situations in which the potassium output increases, in all except one it has thus far been demonstrated that there is actually net secretion. That is to say, under these conditions the potassium clearance has been shown to be greater than the simultaneous glomerular filtration rate. A very important piece of evidence is to be found in the micropuncture studies reported recently by Dr. Phyllis Bott. She observed that potassium virtually disappeared from the urine of the proximal tubule and then reappeared in the urine of the distal tubule.[7]

The fourth reaction which I wish to describe is sodium-hydrogen exchange, which is shown four different times in Figure 2. In view of recent work there seems little reason to question the manner in which this reaction is depicted. At least one can say that the simplest way to describe the experimental data is to consider that a sodium ion from the tubular urine is exchanged for a hydrogen ion from the cell. It should be pointed out that the eventual disposition of this hydrogen ion can be predicted on the basis of simple chemistry and that it is completely dependent upon the composition of urine in the tubule. For example, if bicarbonate is present, the addition of a hydrogen ion will result in the formation of H_2O and CO_2. This is described twice in Figure 2 in order to emphasize that the tubule is probably fairly uniform in terms of this function, even though it was formerly thought that this process was limited to the distal tubule. If there is active tubular synthesis of ammonia, the hydrogen ion will combine with the ammonia molecule and will appear in the final urine as an ammonium ion. If the patient is filtering or, more strictly, is excreting a large amount of buffer acid, here depicted as phosphate ion, the secreted hydrogen ion will combine with the buffer and will now be accounted for in the voided urine as titratable acid.

The source of the hydrogen ion is not depicted in this figure but you will recall that it comes from the hydration of CO_2 in the cells of the renal tubule and that this reaction is enzymatically catalyzed by carbonic anhydrase. This enzyme is inhibited by acetazoleamide, or diamox.® The net effect of the drug is thus an inhibition of the sodium-hydrogen exchange reaction. It is also believed that the over-all exchange reaction can be enhanced by increasing the hydrogen ion concentration within the tubular cell. The precursors of the hydrogen ion are H_2O and CO_2. Obviously, the water concentration is quite constant; but as the result of a rise in pCO_2, as in respiratory acidosis, there is marked stimulation of sodium-hydrogen exchange and this produces increased reabsorption of bicarbonate.

Up to this point we have discussed four tubular mechanisms but it turns out that in so doing we have also described three separate reactions leading to sodium reabsorption. I have attempted some approximate bookkeeping in Table II which is a fairly reasonable estimate of what happens under normal conditions. First, sodium is reabsorbed with fixed anion and this can be easily calculated. Second, sodium is also reabsorbed in exchange for hydrogen, and this can be subdivided into at least four different

categories: as bicarbonate reabsorbed, as ammonium excreted, as titratable acid excreted, and as the free hydrogen ion which appears in an acid urine. The third mechanism for sodium reabsorption is that of sodium-potassium exchange.

TABLE II
SUMMARY OF MECHANISMS OF SODIUM REABSORPTION

Reaction	Amount μ Eq./min.
1. Reabsorbed with fixed anion (mostly Cl^-)	12,000
2. $Na^+ - H^+$ exchange	
a. $NaHCO_3$ reabsorbed	3,200
b. NH_4^+ excreted	20
c. Titratable acid excreted	30
d. Free H^+ excreted (1 ml. urine at pH 5)	0.01
3. $Na^+ - K^+$ exchange, K^+ excreted	50

These are just average rates and do not denote those obtained under conditions of stress. Note that the amount of hydrogen ion which appears in the final urine as ammonium plus titratable acid is very small compared to that which can be accounted for as leading to the reabsorption of bicarbonate. Also note that the free hydrogen ion concentration of the urine is microscopically small compared to the total amount exchanged, but it should be emphasized that this is an extremely important fraction since the buffering capacity of the urine is in large measure determined by the final pH. When we measure urinary acidification in the clinic, we commonly use the term to mean the sum of titratable acid plus ammonia. These quantities are small compared to the amount of bicarbonate reabsorbed but they are very important in terms of total balance. We will come back to this problem later when we discuss adjustments to alkalosis.

With this as background, we may now consider some renal disorders which can be described in terms of the mechanisms just reviewed. The first would be an abnormal reabsorption of sodium with a fixed anion, that is, chloride. This is by all odds one of the most important disturbances that we encounter in clinical medicine. When this reaction goes at an accelerated rate, it leads to edema, as in congestive heart failure, nephrosis, and so forth. When it goes at a decreased rate, there is an exceptional loss of salt, as in Addison's disease. In both instances there may be an associated change in sodium-hydrogen exchange so that the pH of the plasma remains unaltered. The increased rate of sodium reabsorption which leads to edema may sometimes be associated with a decrease in the filtered load. However, this problem is a clinic all by itself and will not be considered further here.

One word might be mentioned, however, about the loss of sodium chloride that is specifically due to renal disease. In patients with chronic renal insufficiency of the classic type—I use "classic type" rather liberally to mean chronic nephritis, nephrosclerosis, pyelonephritis and so forth—an exceptionally large fraction of the filtered sodium is excreted in the urine. In some instances the output of sodium may be quite large and leads to severe sodium depletion. This has been called "salt losing nephritis" but it is problematic whether it should be considered a separate disease entity since it may merely represent a severe form of the salt wastage commonly seen in chronic renal disease. However, in these patients loss of sodium can become extremely important, especially if the dietary intake of sodium chloride is rigidly restricted.

Another situation in which we encounter an exceptional loss of sodium and chloride is in the diuretic phase of acute renal insufficiency. As you know, following the phase of acute oliguria there is usually a diuretic phase characterized by the excretion of large volumes of urine in which the concentrations of sodium and chloride ions are approximately two-thirds of their concentration in the plasma. In most patients the excessive loss of sodium chloride is a transitory phenomenon and complete recovery can be anticipated. However, the diuretic phase calls for adequate replacement therapy to avoid excessive dehydration.

Chronic renal insufficiency is characterized by metabolic acidosis as an outstanding feature of the uremic syndrome. Partly in contrast to what we will say in a few moments, it should be emphasized that the major defect in these patients (those with "classic" renal insufficiency) is probably attributable to a reduction of total renal tissue and, in particular, to a decrease in the glomerular filtration rate. The excretion of urea, phosphate and sulfate is predominantly determined by the filtration rate. As this falls the plasma concentration of each of these components will rise. In general terms, the plasma

level may be expected to increase until a new steady state is reached at which the rates of production and excretion again become equal. Thus the compensation for a fall in the rate of glomerular filtration is an increase in the concentration of each of these substances in the plasma that is filtered. The retention of urea *per se* does not result in any disturbance of acid-base balance. But the simultaneous retention of phosphate and sulfate displaces the bicarbonate ion in the plasma and thus leads to a metabolic acidosis. In addition, the decreased capacity of the kidney to synthesize ammonia contributes to the acidosis by permitting an undue loss of fixed cation, that is, sodium.

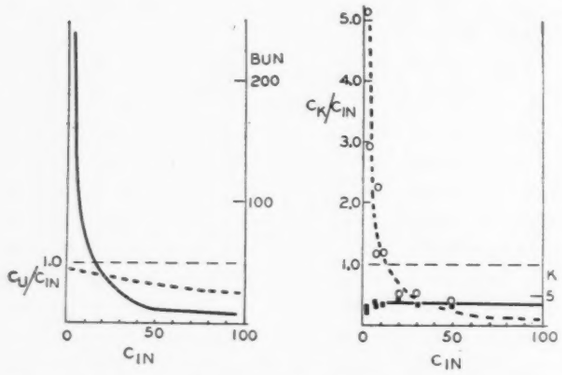

FIG. 3. Comparison of potassium and urea clearances in chronic renal insufficiency.[8] To the right of each figure are the blood levels for blood urea nitrogen (BUN) as mg./100 ml. and for serum potassium (K) as mEq./L. The blood level is indicated by the solid line. To the left are the clearance ratios for urea/inulin (C_U/C_{IN}) and the clearance ratios for potassium/inulin (C_K/C_{IN}). The clearance ratios are indicated by the broken lines. Note that as the inulin clearance (C_{IN}) falls while renal insufficiency progresses, the urea clearance does not exceed the inulin clearance but the potassium clearance becomes much greater than the inulin clearance.

The mechanisms of potassium excretion in patients with "classic" renal insufficiency may be briefly considered at this point. In chronic renal disease of this type elevation of the serum potassium is not very common. This is in contrast to acute anuria which is much more frequently accompanied by significant hyperkalemia. In Figure 3 are summarized the studies on potassium excretion in chronic renal disease which were reported by Bradley and his group.[8] For comparison I have included comparable data on urea. The normal urea clearance is about half the filtration rate. As the filtration rate falls, due to the progress of the renal disease, the ratio of the urea clearance to the filtration rate tends to rise. We will not go into the significance of this rather slight rise but want to emphasize that the ratio does not rise above unity, that is, the urea clearance does not exceed the filtration rate.

How, then, does the patient excrete urea which is being formed at approximately the same rate as in the normal subject? As has already been indicated, this is accomplished by the increase in the plasma concentration so that in each milliliter of plasma filtered at the glomerulus there is a higher urea concentration. Thus chronic glomerular insufficiency eventually leads to a state in which, by virtue of the increase in plasma level, the rate of urea excretion becomes equal to its rate of production.

This mechanism may be contrasted with that for potassium excretion in the same patients. As shown in Figure 3, when the serum levels of potassium are plotted against the inulin clearance, we find absolutely no rise in the plasma level in the patients who were studied. Since these subjects were on a normal diet we may assume that their potassium intake was approximately normal and, therefore, over a long period of time they must have excreted potassium in normal amounts. How, then, do they excrete potassium in the presence of a low filtration rate? The answer is quite evident since the potassium clearance eventually became much greater than the filtration rate in the advanced stages of the disease. In other words, potassium is being secreted by the tubules. While the urea clearance is limited by the filtration rate, this is not the case for potassium. As stated previously, there is reason to believe that tubular secretion is the normal mechanism of potassium excretion. Considering this in terms of chronic renal disease one might say that this particular secretory mechanism is a rather "tough" one. It is one of the last specific renal functions to deteriorate—hence the normal or only slightly elevated serum potassium levels in most patients with chronic renal failure.

The acidosis of "classic" renal insufficiency is due primarily to decreased glomerular function. This is in contrast to the acidosis associated with a much rarer entity known as renal tubular acidosis. Our knowledge of the physiologic disturbances in this condition is largely based on the careful balance studies carried out by Albright and his group.[9] The normal renal response to administration of an acidifying salt

is an increase in the excretion of ammonia and, to a lesser extent, the titratable acid of the urine. Patients with renal tubular acidosis are unable to do this in an adequate manner. That their renal disorder is primarily a tubular dysfunction is indicated by normal levels of blood urea and, when it has been measured, by normal or only slightly reduced filtration rates. The metabolic breakdown of the foodstuffs of a normal diet leads to a slight excess of fixed anions. These patients are unable to keep in proper acid-base balance and develop a metabolic acidosis with a low plasma bicarbonate and a high plasma chloride level. Since glomerular function is normal this type of renal acidosis is not associated with retention of phosphate or sulfate; indeed, in many patients the plasma phosphate is low.

The tubular defect can be considered to be a partial failure of sodium-hydrogen exchange and this, in terms of the mechanisms previously discussed, leads to decreased excretion of ammonia and titratable acid and to increased excretion of bicarbonate. The urine pH is usually found to be between 6 and 7. Since sodium-hydrogen exchange is a mechanism of sodium reabsorption, one might expect that these patients would become depleted of sodium. However, this does not occur to a significant degree and the reason apparently lies in the fact that urinary sodium is replaced by other fixed cations, mostly calcium and potassium. The tubular mechanisms responsible for the hypercalciuria are not well understood and we will not attempt to review this aspect of the problem. However, two consequences of the hypercalciuria should be mentioned because of their clinical importance. The chronic negative calcium balance may be responsible, in part, for the osteomalacia characteristic of the disorder. Linear areas of rarefraction, or pseudofractures, are common and are often associated with pain and discomfort. In addition, hypercalciuria, especially in the presence of an alkaline urine, is associated with the formation of renal calculi.

These patients also have excessive urinary excretion of potassium which may be regarded as another mechanism of conserving sodium and thus maintaining extracellular fluid volume. It is tempting to attribute the increased excretion of potassium to an augmented rate of sodium-potassium exchange by the distal tubule. This has not been conclusively demonstrated for patients with renal tubular acidosis. However, it has been shown that patients with Fanconi's syndrome unequivocally secrete potassium.[10] In terms of acid-base balance this disorder is closely related to renal tubular acidosis. Thus in renal tubular acidosis it is not unreasonable to visualize a failure in the sodium-hydrogen exchange mechanism as compensated for by augmentation in the rate of sodium-potassium exchange. In general terms, the conservation of sodium leads to preservation of the extracellular volume but, in this instance, this is attained at the expense of a major deficit of potassium. Some patients may develop the dramatic paralytic manifestations of the low potassium syndrome.

The treatment of renal tubular acidosis is a direct consequence of the primary physiologic abnormality and involves the use of as simple a substance as sodium bicarbonate. Although vitamin D may also be required to correct the osteomalacia in some instances, the administration of sodium bicarbonate is most dramatic and leads to prompt relief of the symptoms and to correction of the measurable chemical defects.

Several years ago, Conan et al.[11] reported a patient with an extreme degree of hypokalemia which was associated with severe muscular fatigue and periodic episodes of paralysis. The potassium clearance on a normal diet was found to be about 40 per cent of the glomerular filtration rate whereas in normal subjects it is from 5 to 10 per cent. When therapeutic amounts of potassium chloride were added to the diet, the renal clearance of potassium rose and values were recorded which were 50 per cent higher than the glomerular filtration rate. It is clear that this patient was not only losing excessive amounts of potassium but also that this was being accomplished by the secretory mechanism, that is, sodium-potassium exchange. Mader and Iseri (*Am. J. Med.*, 19: 976, 1955) suggest that excessive renal loss of potassium in this case may have been due to oversecretion of aldosterone.*

We have cited instances of failure of the mechanisms for urinary acidification and have pointed out that both glomerular and tubular factors may contribute to the resultant acidosis. Let us now consider failure in the opposite direction, that is, the inability to excrete an alkaline urine. As you know, it is customary to describe the renal compensation for metabolic alkalosis as

* For a discussion of the role of primary aldosteronism in "potassium-losing nephritis" see Conn, *Ann. Int. Med.*, 44: 1, 1956.

the excretion of an alkaline urine with an increased concentration of bicarbonate. If the pH of the urine is higher than that of the plasma, by definition there can be no titratable acidity. The output of ammonium ions will also be vanishingly small. As outlined previously, all these phenomena may be attributed to a relative depression in the rate of sodium-hydrogen exchange.

Two conditions, now well defined, are associated with excretion of an acid urine concomitantly with alkalosis of the extracellular fluid. This so-called paradoxic aciduria occurs either with severe dehydration or with a chronic potassium deficit. The role of dehydration is best illustrated by an experiment by Gamble[12] in which pyloric obstruction was produced in the dog. This resulted in metabolic alkalosis due to vomiting of large amounts of hydrochloric acid in the gastric juice. In the early stages the kidney partially compensated for this by excreting an alkaline urine. After a few days, however, despite progressive elevation of the serum bicarbonate level, the urine decreased in volume and its reaction became very acid. In this instance the aciduria was clearly due to acute dehydration since it was rapidly corrected by the parenteral administration of isotonic sodium chloride solution.

In attempting to evaluate the role played by the multiple physiologic factors involved in this situation, it is important to remember one of the fundamental characteristics of an alkaline urine, namely, that it must contain a very high concentration of fixed cation. Since the carbon dioxide tension (pCO_2) of the urine is relatively constant, it is an inevitable consequence of the relationships described by the Henderson-Hasselbalch equation that a urine of high pH must have a high concentration of bicarbonate anion, and this in turn must be accompanied by a comparable concentration of cation. This is predominantly sodium, although at times the potassium level may be quite high. The obligatory excretion of large amounts of sodium in an alkaline urine can be considered as resulting from an alteration in tubular function, namely, a relative decrease in the rate of sodium-hydrogen exchange. This response occurs during the initial renal compensation for metabolic alkalosis and subsequently leads to a diminution in extracellular fluid volume with eventual hemodynamic adjustments which probably involve a decrease in the renal plasma flow and the rate of glomerular filtration. Irrespective of the relative role attributable to each of these factors, the final result is conservation of sodium and excretion of an acid urine. Since vomiting leads to both alkalosis and dehydration, the frequency with which this type of paradoxic aciduria is encountered in clinical practice is probably much greater than is generally realized.

The second situation in which there is failure to alkalinize the urine during extracellular alkalosis occurs as a result of potassium depletion. This condition takes a fairly long time to develop, is not necessarily associated with dehydration, and does not respond to replacement therapy with sodium chloride. The underlying mechanisms are currently being investigated in a number of clinics. Although some of our concepts are apt to change, the present status may be briefly summarized. The changes which occur in the composition of extracellular fluid during chronic potassium depletion are a rise in bicarbonate, an elevation of the pH, and a variable degree of depression in the level of potassium. The behavior of intracellular fluid is quite different. While intracellular potassium is low and is partly replaced by sodium, the intracellular changes in pH are the opposite of those that occur in the extracellular compartment, that is, there is an intracellular acidosis. Consistent evidence concerning this phenomenon has been obtained from a number of different types of experiments—balance studies in rats, direct measurements of muscle bicarbonate in rats, and balance studies during experimental potassium depletion in man. Of course, there are some conditions in which potassium depletion is not associated with an abnormality in acid-base balance. But the point to be emphasized is that when extracellular alkalosis does develop in association with a negative potassium balance, it is accompanied by an intracellular acidosis.

It is implicit in this concept that the administration of potassium salts can be regarded as a specific type of therapy for the correction of the acid-base disturbance. There are now many clinical reports in which this has been observed. Perhaps the most common condition arises on the surgical wards when a negative potassium balance results from extensive loss of gastrointestinal secretions combined with a decrease in dietary intake of potassium.

Our knowledge of the mechanisms by which

potassium acts is in large part due to the work of Darrow and Cooke and their collaborators[13] who were able to determine the relative roles played by the kidney and by the intracellular environment. When potassium is administered to a potassium-depleted animal, this ion is rapidly accumulated by the cells in partial exchange for sodium. However, there is a simultaneous change in acid-base distribution which can most simply be described as the migration of some of the administered potassium into the cell in exchange for hydrogen ion. By this exchange the pH within the cell tends to rise while in the extracellular fluid it tends to fall. Correction of the extracellular alkalosis is reflected in a fall in the serum bicarbonate toward normal levels. That the kidney is in this instance not essential for correction of the acid-base disturbance is clearly demonstrated by the fact that a similar result is obtained in the nephrectomized animal.

However, it should be pointed out that in hypokalemic alkalosis, as observed in man, the kidneys play a very important role which permits the extracellular level of bicarbonate to be maintained at abnormally high concentrations. It may well be asked what it is that tells the kidneys what to do. Here we have a disturbance that is characterized by an extracellular alkalosis and an intracellular acidosis, a sort of schizophrenia amongst the electrolytes. Several workers have suggested the possibility that the cells of the renal tubules might share in the general cellular response to potassium depletion and by becoming more acid might thus directly regulate the rate of sodium-hydrogen exchange. This would lead to increased reabsorption of bicarbonate and excretion of an acid urine. Darrow and his associates were unsuccessful in their attempts to demonstrate by direct tissue analysis that the tubular cells were more acid in potassium-deficient animals. However, more recently Dr. Anderson in our laboratory has been able to show in an *in vitro* system of kidney slices that the level of intracellular potassium is a major determinant of the cell pH. Slices depleted of potassium are much more acidotic than those with a normal potassium content.

A dramatic change in renal function is observed when a patient with hypokalemic alkalosis is treated with potassium. The urine soon becomes alkaline in reaction, indicating the excretion of large amounts of bicarbonate. Thus the disturbance in acid-base metabolism is corrected in part by the cation exchanges of the intracellular fluid and in part by the changes in external balance that result from the alteration in the rate of sodium-hydrogen exchange by the renal tubule. This, in turn, may depend upon a primary correction of the intracellular electrolyte composition of the tubular cells.

In addition to the examples that have been cited there are undoubtedly many other types of renal dysfunction that are characterized by abnormalities in electrolyte transport. It should be emphasized that most of these disturbances can be considered only in rather general descriptive terms since so little is known about the discrete reactions responsible for tubular transport. However, these gaps in our knowledge should not obscure the fact that management of these disorders may often be both simple and successful if based on critical diagnostic concepts.

We shall now turn from a consideration primarily of mechanisms to a discussion of a disease entity, the Fanconi syndrome.

DR. STANLEY E. BRADLEY: Dr. Mudge has asked me to discuss the Fanconi syndrome because it illustrates the consequences of a variety of discrete renal tubular dysfunctions. In this disorder diminished renal tubular reabsorption of glucose, of amino acids and of phosphate gives rise to persistent glycosuria in the face of normal blood levels of glucose, to striking aminoaciduria without change in the plasma amino acid concentration, and to heavy phosphaturia. These disturbances appear to be responsible for the clinical manifestations that lead in children to rickets and to retardation of growth, and in adults to osteomalacia with multiple pseudofractures that ultimately result in invalidism and complete incapacity.

The devastating effects of this disorder in childhood were strikingly displayed in Claire J. when she was admitted to the Babies Hospital in October, 1950, at twenty-six months of age. Approximately six months before admission she became irritable; cried when handled, apparently in pain; and these manifestations worsened as time went by. Finally, her mother took her to the family physician who found that the child had severe rickets. She was given large amounts of vitamin D and ultraviolet radiation, with some but not much improvement. The child suffered from repeated upper respiratory infections and was admitted to another hospital with pneumonia some two months before admission to this hospital. At that time persistent glycosuria was discovered. Her mother said

that the child began to put out a larger volume of urine about this time, and has continued to do so. Following recovery and discharge she concontinued to do badly. She did not gain weight, became more and more irritable and, finally, a few weeks before admission, the mother noted a deformity of the right wrist. X-ray examination revealed fractures involving both the radius and the ulna. The family physician then sent the child to this hospital for study with the diagnosis of Fanconi's syndrome.

She was a dwarfed, irritable little girl, lying in bed unable to sit up or roll over, whimpering when handled. She presented the classic signs of rickets, with frontal bossing, occipitoparietal flattening, flaring and beading of the ribs and bowing of the lower extremities. The ends of the shafts of the long bones were definitely enlarged. X-ray examination bore out the clinical diagnosis of rickets, showing cupping and fraying of the ends of the shafts, widening of the epiphyseal cartilage, generalized demineralization and some trabeculation of bone structure. There were multiple fractures of the upper extremities which produced serious deformities, including ulnar deviation of both hands, particularly noticeable on the right. In addition a large, firm liver was palpable to the level of the umbilicus. The spleen tip became palpable later in the course of her illness.

Further investigation revealed persistent glycosuria, proteinuria (2 to 4 plus) with microscopic hematuria and pyuria on occasion. The specific gravity of the urine appeared to be fixed between 1.010 and 1.012. Studies by Dr. Ruth Harris revealed a remarkable loss of amino acids in the urine, amounting to as much as 8 gm. per day. Such an excretion is fifteen to thirty times the normal (200 to 400 mg. per day) in adults. Dr. Harris also found an unusually large number of amino acids in the urine, fifteen in contrast to the three to seven usually detected by her method. These changes had occurred in the absence of any abnormality in the plasma glucose or amino acid content. However, the chemical composition of the blood was grossly abnormal in many other respects. The plasma bicarbonate concentration was 10 mEq./L. At no time during the subsequent course has it been found above 18 mEq. and on occasion it has fallen as low as 5 or 6 mEq./L. The reduction in the bicarbonate concentration was associated with a rise in plasma chloride to 125 mEq./L. The phosphate concentration was greatly reduced, to 1.9 mg. per cent. Plasma sodium content ranged between 130 and 140 mEq./L. and the potassium level was 3.6 mEq./L. The plasma calcium concentration was within normal limits. The pH of the serum was 7.3.

The loss of glucose and amino acids in the urine appeared to be directly attributable to impaired tubular reabsorption since both glomerular filtration rate and renal plasma flow (PAH clearance) fell within normal limits at 45 ml. per minute and 120 ml. per minute respectively. We were rather surprised to find that the maximal glucose reabsorption (glucose Tm) amounted to 207 mg. per minute, a value definitely above normal for a child of this age and size, suggesting that the mass of active tubular tissue was not reduced. The large excretion of amino acids was associated with sufficient output of phosphate buffer and ammonium ion to maintain an alkaline urine. The phosphate clearance averaged 33 ml. per minute, approximately 73 per cent of the filtration rate (in normal persons, the phosphate clearance rarely exceeds 12 per cent of the filtration). It is possible that impairment of the reabsorptive processes may have contributed to the loss of phosphate (and presumably also of calcium) and may have interfered with adequate acidification of the urine but quantitative data on these points were not obtained.

Liver function was definitely impaired. There was a retention of bromsulphalein® of 18 per cent at the end of thirty minutes. The prothrombin time was prolonged (twenty-four seconds) and the blood sugar did not rise following administration of a small dose of adrenalin.® However, the serum bilirubin concentration was 0.8 mg./100 ml. and the cephalin flocculation test gave negative results.

The combination of hepatic and renal involvement in this child suggests the possibility that Fanconi's syndrome may arise as the result of a widespread disorder of cellular metabolism. There is much confusion on this point and I have no doubt that confusion will persist until we have a much better understanding of the condition than we now possess. It seems likely that a number of fundamentally disparate disorders that have so far escaped differentiation have been brought together under the diagnostic label of "Fanconi's syndrome." In one form, which appears at present to be distinctive, usually referred to as cystinosis or Lignac's

disease, deposits of cystine crystals in the liver, spleen, bone marrow, lymph nodes and other tissues suggest that a defect in the metabolism of cystine may be at fault. Some workers have claimed that such deposits are detectable in all cases of Fanconi's syndrome but this view is losing ground even among those who have been its most ardent supporters. A second form of the disorder may possibly arise as a result of renal disease. Certainly renal dysfunction is an important determining factor whether it is the result of an intrinsic lesion or the local manifestation of a more generalized disturbance.

A defect in renal tubular function undoubtedly accounts for the heavy losses of glucose and amino acids in the urine. The site of amino acid reabsorption in the tubules is not known but there is good evidence that glucose reabsorption occurs in the proximal segment. It may be inferred from the relationship between glycosuria and aminoaciduria in Fanconi's syndrome that amino acids are also reabsorbed in the proximal convoluted tubule and that a single lesion in this portion of the nephron may account for the disorder. The diuresis and cation loss resulting from the escape of glucose in the urine together with the loss of electrolyte secondary to the large excretion of acid might indeed be responsible for the development of hyperchloremic acidosis, hypophosphatemia and calcium deficit so prominent in many patients. It might also be argued that the continuous waste of amino acids by the kidney during a period of active growth might prove injurious to the liver in some manner, ultimately giving rise to the cirrhotic changes frequently demonstrable at death.

The opinion that Fanconi's syndrome is primarily a renal disease has found some support from a recent study[14] of the micro-anatomy of the nephrons isolated by microdissection from the kidneys of two patients with the condition. Clay, Darmady and Hawkins[14] report that the proximal convoluted tubule is usually shortened and attached to the glomerulus by an attenuated, atrophic, narrow segment which resembles a "swan's neck." The cells of the "swan-neck lesion" appear to be incapable of normal activity and it is possible that impaired reabsorption of glucose and amino acids in this portion only of the proximal segment may be sufficient to set in motion a complex train of dysfunctions that culminates in Fanconi's syndrome. The frequent history of consanguinity and the strong evidence of a familial tendency (Dent[15] has observed a characteristic aminoaciduria prior to the appearance of the syndrome in siblings of patients with the disorder) provide substance for the belief that the change in the nephron may be an hereditable anomaly.

A lesion of this kind could conceivably account for the troubles suffered by patient Claire J. It is possible that a defect in glucose reabsorption affecting only a small proportion of the tubules could result in glycosuria without any significant abnormality of the maximal rate of glucose reabsorption. The elevated value for glucose Tm in Claire J. is not inconsistent with such an interpretation. Under these circumstances one would expect that the maximal reabsorption of the various amino acids would also be normal. To test this possibility we gave the child 70 ml. of a fibrin hydrolysate (aminosol®) intravenously. The increment in the amount and number of amino acids in the urine was no greater than in the normal[16] suggesting that the renal mechanisms for handling unusually large amounts of amino acids were intact. Unfortunately we have no data on the crucial question of whether the tubules handle electrolytes normally. Few studies of this kind have been made in other patients and those that have been made are difficult to interpret in general terms owing to the fact that widespread tubular damage may ultimately develop. Thus defects in phosphate and urate reabsorption, creatinine and p-aminohippurate excretion, and ammonia synthesis reported in other patients[10] indicating widespread lesions of the tubule as a whole could be ascribed to damage resulting from the ill effects of persistent aminoaciduria and glycosuria. Likewise, lack of positive proof that losses of phosphate and cation are initially secondary to the proximal segment disorder may simply be an unfortunate consequence of our inability to recognize the disorder before it is far advanced.

These arguments are not acceptable, however, and it must be admitted that the evidence favoring an isolated tubular lesion as the basis for Fanconi's syndrome is inadequate. Indeed, Dr. Taggart has already indicated that renal glycosuria may persist throughout life without interfering in any important manner with normal urine formation and renal regulation of the plasma composition. Likewise, a continuous and copious excretion of amino acids does not result in excessive excretion of calcium, sodium

or potassium. In congenital cystinuria, for example, as much as 1 gm. of cystine, in association with smaller amounts of lysine and arginine, may be excreted each day without clinical manifestations other than those that may arise from cystine stone formation. In Wilson's disease, also, aminoaciduria occurs in the absence of biochemical abnormalities like those encountered in Fanconi's syndrome. Renal tubular lesions resulting from intrinsic renal disease, such as pyelonephritis or chronic diffuse glomerulonephritis, rarely give rise to aminoaciduria and glycosuria even when a load is imposed upon the tubules by intravenous infusion of glucose or fibrin hydrolysate.[16] It seems likely, therefore, that Fanconi's syndrome has its origin in a complex disturbance of cellular physiology in general and that renal dysfunction is a secondary and not a primary manifestation. The multiple derangements of tubular function have not yet been defined with sufficient precision to permit any more than a superficial description of the major changes. The course of events, the origin of the "swan-neck lesions," the factors involved in producing progressive damage and the inter-relationship between hepatic and renal disorders remain obscure. The information available does provide a basis for diagnosis and for more effective management. Further clarification will undoubtedly increase the efficacy of therapy and even perhaps show the way to curative measures.

The recent development of new tools such as paper chromatography and saturation methods, by which more exact evaluation of the mechanisms of amino acid reabsorption is possible, has opened up a whole new field of research. Tubular transfer of different amino acids relative to one another, to pH, to various electrolytes, to water and to other organic substances can now be worked out with precision. It is possible that data of this kind will clarify amino acid metabolism by tissues elsewhere in the body, just as the growing body of knowledge regarding metabolic activities of the cells in general has improved our understanding of kidney function.

Dr. Mudge: Are there any questions?

Dr. Yale Kneeland: Would Dr. Harris discuss the mechanism of acidosis in Fanconi's syndrome? Is it due to a failure of the acidification mechanism or to the excessive load of fixed anions which are excreted?

Dr. Ruth Harris: This child is unusual in that her output of alpha amino nitrogen is much greater than in most of the reported cases. It ranges between 20 and 27 per cent of the total urinary nitrogen. (Normal values are 1 to 2 per cent of total urinary nitrogen.) While the anion load is partially associated with increased ammonium excretion and also is partially buffered by an increase in urinary titratable acid, she nevertheless fails to acidify the urine normally. Her urinary pH is about 6 when her plasma pH is as low as 7.2. A normal child would excrete a much more acid urine under these conditions. Extensive defects of the distal tubular system have therefore been postulated.

During the four and a half years of observation, no cystine crystals have been found in her corneas or bone marrow. It is probable that this syndrome is not related to cystinosis in this patient.

In several conditions, namely, galactosemia and lead poisoning, aminoaciduria has been noted to accompany glycosuria. This disappears when the noxious agent is eliminated from the body system, a sequence which points to a close relation between amino acid excretion and renal loss of sugar. Also, in resistant rickets of unknown cause, cure eliminates pre-existing mild aminoaciduria. Recent studies of Wilson's disease seem to indicate that the aminoaciduria may be secondary to toxic effects of copper deposition in kidney tissue. Perhaps, then, this proximal tubular abnormality is always secondary to a specific type of noxious agent which may also have other damaging effects on tissue metabolism.

Dr. C. T. Vicale: What is the best treatment for the Fanconi syndrome?

Dr. Harris: Unfortunately, none of the patients reported has ever been cured. Doses of vitamin D, ranging from 50,000 to 600,000 units, have caused healing of the rickets for short periods of time; additional phosphate as well as sodium and potassium in the diet have helped maintain more normal blood levels and have decreased the acidosis. General measures to improve and support nutrition are obviously indicated. The clinical manifestations vary from patient to patient, and one must tailor the treatment accordingly. A search for the basic defect and correction of this defect is still the main hope for the solution of this problem.

SUMMARY

Dr. Gilbert H. Mudge: In this Clinic some of the mechanisms of renal tubular transport

have been reviewed both in relation to normal function and to specific disturbances observed in various types of renal disease. Since there are many separate mechanisms of normal tubular function, there are correspondingly many types of dysfunction.

Glucose is normally completely reabsorbed in the proximal tubule. The physiologic concepts of threshold and maximal rate of tubular transport (Tm) are reviewed. The criteria for the diagnosis of true renal glycosuria are critically evaluated. The pathogenesis of this disorder is considered in terms of two possibilities—first, that it is due to a homogeneous population of defective nephrons and, second, that it is due to heterogeneous population characterized by marked variations in the functional balance between the glomerulus and tubule of individual nephrons. A review of the available physiologic studies yields no single explanation for renal glycosuria and it is therefore suggested that this syndrome may constitute a group of disorders with different fundamental abnormalities.

Some of the tubular mechanisms of electrolyte transport are reviewed and four reactions are considered in detail. These are: (1) the reabsorption of sodium with a fixed anion; (2) the reabsorption of potassium; (3) the secretion of potassium; and (4) the exchange of sodium for hydrogen ions. A number of different clinical disorders are evaluated in terms of the role played by each of these mechanisms.

Failures of the mechanisms for acidification of the urine are commonly encountered; failure of alkalinization is less frequently recognized. Two types of paradoxic aciduria may now be distinguished; first, that associated with dehydration, and second, that associated with long-standing potassium depletion. In the former, hemodynamic factors are of major importance, while in the latter intracellular acidity plays a critical role.

The Fanconi syndrome represents a renal disease characterized by multiple defects in tubule function. Abnormalities in the reabsorption of glucose, amino acid and phosphates are recognized. In attempting to evaluate this disturbance it is emphasized that the primary abnormality in renal function must be distinguished from secondary disturbances. The therapy of this syndrome is briefly reviewed.

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Clinico-pathologic Conference

Arthritis, Polymyositis and Polyneuritis

STENOGRAPHIC reports, edited by Amoz I. Chernoff, M.D., and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

PATIENT F. H., a forty-seven year old white married housewife, was admitted to the medical service of Barnes Hospital on May 28, 1955, complaining of arthritis of two years' duration and "dead" feet of nine weeks' duration.

The patient had apparently been in good health until two years prior to admission when she began having pain, a sensation of heat, and swelling of both feet. One month prior to the onset of symptoms two of her six children were killed in an automobile wreck. A few weeks after the onset of symptoms, the left knee and both hips and elbows became hot, swollen and tender intermittently. Night sweats were frequent. One and a half years prior to admission she received one gold injection. Iron and vitamins were given for an anemia said to have been present. Six months later arthritis in her wrists and finger joints developed. During the half year prior to admission, she received multiple antibiotics, sulfonamides and hydrocortisone, with some improvement. However, facial edema began to appear and administration of hydrocortisone was stopped five weeks before the patient's entry to the hospital. Nine weeks prior to admission, she had a sudden onset of numbness, burning and weakness of both legs and thighs. These symptoms gradually subsided but residual burning, tingling and foot drop bilaterally persisted. Five weeks later the patient noted similar symptoms in her right forearm which gradually subsided. About the same time redness of the conjunctivas developed along with photophobia which persisted. During the four weeks prior to admission the patient suffered constantly from marked weakness, anorexia and fever. Frequently throughout her illness she became depressed and cried. For several months she had had a poor food intake and during a period of two years she had lost twenty-seven pounds.

Her past history was unremarkable and the family history non-contributory.

Physical examination at the time of entry revealed the patient's temperature to be 38.2°C.; pulse, 128; respirations, 20; and blood pressure, 105/85. She appeared to be well developed, but with evidence of weight loss, and acutely and chronically ill. There were marked arthritic deformities of both hands, most pronounced on the right, with questionable subluxation of the metacarpophalangeal joints. Minimal deformities of the knees, ankles and elbows were present. The skin was clear. No lymph nodes were felt. The conjunctivas were markedly reddened bilaterally without exudate. The pupils reacted to light and accommodation. The optic fundi were not remarkable except for blurring of the disc margins without elevation. Whitish gray 5 mm. shallow ulcerations around the edge of the tongue were seen. Examination of the neck, lungs, heart and abdomen was not remarkable. There was marked weakness and atrophy of the interossei, wrist extensor and foot extensor muscles. There was wrist drop and foot drop bilaterally. Ankle jerks were absent bilaterally, and the knee jerk on the left was diminished. There was diminished sensation to pain and light touch along the lateral aspects of the feet and legs, the dorsum of the right foot, and the ulnar distribution of the right hand. Vibratory and position senses were diminished in the hands and feet.

The laboratory data were as follows: blood count: hemoglobin, 12.0 gm. per cent; white blood cell count, 10,800 per cu. mm.; differential count: one eosinophil, six band forms, seventy-five segmented forms, sixteen lymphocytes and two monocytes. The red blood cells showed slight anisocytosis, and the platelets appeared adequate. Blood counts done seven

days after admission revealed a packed cell volume of 32 per cent, hemoglobin of 10.2 gm. per cent, red blood cell count of 3.68 million per cu. mm.; red blood cell constants calculated from these figures were: mean corpuscular volume, 87 cu. microns; mean corpuscular hemoglobin, 28 gamma gamma; mean corpuscular hemoglobin concentration, 31 per cent. No L.E. cells were seen on two examinations. Urinalysis: on repeated examination the specific gravity ranged from 1.010 to 1.030; pH, 4.5 through 7.5; protein, trace to 1+; sugar, 0 to trace; microscopic, two to four white blood cells and an occasional red blood cell were seen on several examinations. On one examination a few hyalin casts were seen. Blood chemical determinations: non-protein nitrogen, 15 mg. per cent; fasting blood sugar, 77 mg. per cent, uric acid, 2.8 mg. per cent; total serum protein, 4.7 gm. per cent; albumin, 2.6 gm. per cent; globulin, 2.1 gm. per cent; cephalin cholesterol flocculation, 1+; thymol turbidity, 12.7 units. Bacteriologic studies: tongue and throat cultures revealed normal flora. Two blood cultures showed no growth. A stool culture revealed no pathogens. One urine culture was reported as growing confluent coliform organisms. The electrocardiogram was interpreted as showing an abnormal form of ventricular complex, sinus tachycardia and prolonged P-R interval. Roentgenographic examination of the chest revealed bilateral apical pleural thickening as well as evidence of fibrosis of the left upper lobe. Splenic calcifications were identified. The roentgenologist's interpretation was "minimal fibrotic tuberculosis of the left upper lobe with bilateral pleural thickening." Roentgenograms of the hands and feet revealed juxta-articular demineralization, soft tissue swelling and narrowing of the joint spaces most marked about the interphalangeal joints. The roentgenologist's interpretation was "rheumatoid arthritis involving both hands and feet."

The patient was started on therapy consisting of bedrest, a high caloric diet, and a product containing para-aminobenzoic acid, sodium salicylate and ascorbic acid. Shortly thereafter multiple vitamins and vitamin B_{12} in doses of 1,000 μg. intramuscularly per day were started. Temperature ranged between 38° and 39°C. daily. On the fourth hospital day a confluent erythematous maculopapular eruption was noted on the right buttock and posterior thigh which was thought by some observers to be due to the patient lying on her back and the accumulation of perspiration. Because of symptoms of slight dysuria and a white blood cell count of 14,800 per cu. mm., a urine culture was taken on the fourth hospital day and the administration of penicillin and streptomycin was begun. Coliform organisms grew out on the urine culture, but repeat cultures four days later were sterile. The white blood cell count dropped to 8,400 per cu. mm., but there was still a slight shift to the left in the neutrophils. During hospitalization, the patient's main complaints were of paresthesias. Her joints bothered her very little. She gained weight and seemed to be improving gradually. Her fever, however, was unchanged. On the twelfth hospital day she was seen by an ophthalmologist who prescribed ½ per cent hydrocortisone eyedrops as treatment for what he diagnosed as episcleritis. On the thirteenth hospital day, skin and muscle biopsy specimens were taken from the right leg. The pathologist's report on the muscle was "polymyositis"; no diagnosis was made on the skin specimen. On the sixteenth hospital day treatment with meticortin® 30 mg. per day intramuscularly was begun. There was marked subjective and objective improvement; paresthesias disappeared and the temperature dropped to normal within twenty-four hours. On the seventeenth hospital day the patient complained of anterior chest pain which radiated to the left arm. This was relieved by codeine. Later that evening she complained of aching all over, particularly in the chest. The pain in the chest was aggravated by movement of the rib cage. There was no cough, sputum or hemoptysis at this time, and examination of the chest revealed no abnormalities. She obtained some relief from her pain after taking 0.6 gm. of aspirin. At 4:30 A.M., June 15, 1955, a nurse found the patient dead.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: I should like to begin this conference by having Dr. Powers review the roentgenograms.

DR. WILLIAM POWERS: The official interpretation of the chest films indicated the presence of minimal fibrotic tuberculosis in the left upper lobe. In my opinion, however, the lung fields were clear. The heart was normal in size and the bony thorax showed no abnormalities. The spleen appeared normal in size and there was evidence of calcification in the splenic area. The

most interesting changes were in the hands and feet. Narrowing of the joint spaces with some erosion of the cortices in the interphalangeal joint spaces and with juxta-articular demineralization were seen. These changes are those of severe rheumatoid arthritis. There was no fusion of the joints and no joint deformities were noted except for a slight flexion deformity of the fifth finger of the right hand. No other significant changes were seen.

DR. REINHARD: Are there any differences between the roentgenographic appearances of the joints in rheumatoid arthritis and in the variety of arthritides or arthralgias that one encounters in association with the so-called collagen diseases?

DR. POWERS: Yes, there are differences, but I believe this pattern is typical of rheumatoid arthritis with actual joint destruction.

DR. REINHARD: Dr. Duden, the hospital record contains no precise description of the patient's joints, except to say that she had rheumatoid arthritis in the joints of her fingers. I would like you to confirm the fact that, clinically, these were typical deformities of rheumatoid arthritis.

DR. CHARLES DUDEN: The patient presented the classic joint changes of rheumatoid arthritis, even to the extent of having marked ulnar deviation of the hands.

DR. REINHARD: Dr. Kingsland, may we accept the diagnosis of rheumatoid arthritis without further discussion or are there other diseases which may produce joint changes indistinguishable from rheumatoid arthritis?

DR. ROBERT KINGSLAND: The only one I know of which may produce changes closely resembling rheumatoid arthritis is lupus erythematosis.

DR. REINHARD: Do you believe that lupus erythematosis produces joint changes that are in some cases practically indistinguishable from rheumatoid arthritis?

DR. KINGSLAND: Not only practically, but actually indistinguishable both from the standpoint of the physical appearance as well as the roentgenographic characteristics of the involved joints.

DR. REINHARD: Throughout the patient's stay in the hospital her temperature chart showed almost daily elevations to between 39° and 39.5°C. It is my impression that the febrile response was out of proportion to the degree of arthritis present at the time of admission. Dr. Duden, do you think this patient had acute active arthritis or were these mainly the deformities of old rheumatoid arthritis.

DR. DUDEN: I thought she had acute active arthritis but I was not at all convinced that the magnitude of the fever was solely the result of arthritis. I believed there might possibly be some other factor.

DR. REINHARD: Would the degree of fever and the profuse sweats that she was having be strongly against rheumatoid arthritis?

DR. DUDEN: There was no doubt in my mind that she had rather active rheumatoid arthritis. I did not think, however, that the activity of the process was of such a degree as to account for all of her fever and sweats. It was for this reason that further diagnostic procedures were undertaken.

DR. REINHARD: Dr. Kingsland, I wonder if you would comment on the visceral manifestations of rheumatoid arthritis. What visceral manifestations are observed in rheumatoid arthritis uncomplicated by any other disease entity?

DR. KINGSLAND: I believe the most common lesion, exclusive of the involved joints, is the subcutaneous nodules, followed much less frequently by pleuritis, carditis (pericarditis, endocarditis and myocarditis) and renal involvement.

DR. REINHARD: Dr. Luse, would you now discuss the skin and muscle biopsy specimens.

DR. SARAH A. LUSE: The skin section was entirely normal. Examination of the muscle biopsy specimen revealed a rather diffuse infiltrate which was present between and surrounding the individual muscle fibers. This infiltrate was made up, for the most part, of lymphocytes and plasma cells. No eosinophils were noted. Occasionally, single fibers of muscle showed an intense eosinophilia and also on occasion a granularity suggesting focal degeneration. In one region there was a distinct infiltration of lymphocytes and plasma cells within the vessel walls. Elsewhere the vessels were essentially normal. In the presence of normal skin sections the lack of eosinophils is certainly against dermatomyositis. The absence of a diffuse interstitial infiltrate separating bundles of muscle fibers as well as the absence of fibrosis in the region of the vessels is uncommon in the type of myositis usually observed in rheumatoid arthritis. The infiltrate in this patient's biopsy specimen is somewhat more diffuse and marked than I have seen in lupus, although certainly the pathologic manifestations in lupus may vary qualitatively and quantitatively in individual

cases. There is insufficient evidence here to make a definite diagnosis of a particular type of myositis. One would certainly want to see more sections than are available to determine whether the alterations of the intima characteristic of periarteritis might be seen in some of the deeper vessels. On the basis of the biopsy slide, however, I think we are obliged to make a diagnosis only of a diffuse myositis of unknown type.

DR. REINHARD: From the biopsy material we can only state that the patient had a rather marked polymyositis of a type that is compatible with, although not perfectly typical, of dermatomyositis. There was, however, no skin involvement in this particular case. The biopsy specimen was also compatible with the type of secondary myositis seen in other connective tissue diseases. Dr. Nickel, let us concentrate our attention on primary polymyositis, or dermatomyositis, if you prefer the term, as distinguished from the interstitial polymyositis secondary to rheumatoid arthritis or to one of the other so-called collagen diseases. Would you first discuss the terms "dermatomyositis," "polymyositis" and "neuromyositis." What do these terms mean? Do they all apply to the same disease, merely emphasizing the tissues that are involved, or are they different entities?

DR. JAMES F. NICKEL: These terms simply designate the involved tissue. We refer to polymyositis when there is no evidence of skin involvement, an inflammatory condition involving primarily the muscles. Dermatomyositis refers to involvement of both skin and muscle. Neuromyositis is used to designate nerve and muscle involvement.

DR. REINHARD: Do you think these are all diseases of similar or comparable etiology?

DR. NICKEL: There has been a good deal of debate about this. I think we are dealing with one or two general processes. In the literature fairly good evidence exists for the entity of primary idiopathic polymyositis. Cases have been reported with both skin and nerve involvement. On the other hand, there is a nodular type of myositis, an interstitial myositis, which is associated with various collagen diseases such as rheumatoid arthritis, rheumatic fever, scleroderma and lupus erythematosis. I believe we can place the various examples of polymyositis into one of these two general categories.

DR. REINHARD: Would you tell us whether you believe that we should consider a diagnosis of dermatomyositis with polymyositis, or are there any features of this case that would make you think that this is not the correct primary diagnosis. Dr. Luse has already mentioned that the biopsy specimen was not typical, especially in view of the lack of eosinophils.

DR. NICKEL: I believe the findings in our patient are not at all inconsistent with what has been designated as chronic polymyositis by Adams, Denny-Brown and Pearson. The pathologic process is visualized as a diffuse infiltration of peripheral muscles by lymphocytes, plasma cells and histiocytes. There are certain features of chronic polymyositis which are rather striking. Chronic polymyositis is more common in adults. In many instances in the female the onset of the disease has occurred at the time of the menopause. The onset is characterized by vague prodromal symptoms, such as malaise and fatigue. Gradually, weakness of the lower extremities, particularly in the thigh muscles, becomes manifest. Patients may complain of a sensation of tightness or weakness in the thighs with some difficulty in arising from the sitting position. Later on more peripheral muscles are involved and edema may appear. Finally the muscles of the upper extremity and, terminally, the muscles of the neck, larynx and pharynx and diaphragm present similar changes. Pain and tenderness may be slight or absent. If the process goes on long enough, the swollen muscles become atrophic and fibrotic contractures may ensue which are indistinguishable from similar changes commonly associated with rheumatoid arthritis. Dermatologic lesions are fairly rare. Usually no nerve involvement is present. There are, however, scattered reports of peripheral neuropathy with fairly symmetric sensory involvement such as described in the protocol of the patient under discussion. However, histologically, this is not believed to be true neuritis.

DR. REINHARD: Would not the peripheral neuropathy be more compatible with other types of connective tissue disease? One point which appears to be rather strongly against a diagnosis of primary polymyositis or of dermatomyositis, is the fact that the roentgenograms seem to show very definite bone and joint destruction. This is a true arthritis. Therefore, it seems to me that if one makes the diagnosis of dermatomyositis or primary polymyositis, one has to diagnose an independent type of joint disease. What would happen if a patient had dermatomyositis plus rheumatoid arthritis?

DR. NICKEL: I believe that the roentgeno-

grams showed primarily some narrowing of the joint spaces and some demineralization, which, of course, is compatible with a history of immobilization of the extremities and fibrotic contractures from any cause. I do not think there is anything more specific in these films for rheumatoid arthritis than for polymyositis. Polymyositis, however, is a rare disease.

DR. REINHARD: Dr. Power, do you think you could get this much narrowing of the joint spaces just from immobilization?

DR. POWERS: I think the roentgenograms showed some osseous involvement with destruction of cartilage and bone which suggests primary arthritis rather than immobilization alone.

DR. REINHARD: Dr. Becker, what is episcleritis? Can you tell us what significance episcleritis may have in terms of the patient's general disease?

DR. BERNARD BECKER: The sclera is a relatively acellular structure consisting of interlacing collagen bundles. It is subject to inflammatory diseases of two major types: a deeper granulomatous disease arising from underlying involvement of the uveal tract and a superficial inflammatory reaction called "episcleritis." The latter condition is frequently found in association with rheumatoid arthritis and more recently has been reported in disseminated lupus, dermatomyositis and other collagen diseases. It responds well to local steroid therapy. I am afraid that the presence of episcleritis offers little help in differentiating various collagen diseases.

DR. REINHARD: Dr. Becker, the term dermatomucomyositis has crept into the literature to describe patients in whom there is mucous membrane as well as skin involvement in myositis. It is my understanding that usually the mucous membrane involvement is limited to the larynx or the pharynx. In dermatomyositis, to your knowledge, has involvement of the conjunctivas or the mucous membranes of the eyes ever been noted? This patient did not have it, but does it occur?

DR. BECKER: In my experience the mucous membranes of the eye have not been involved in dermatomyositis. It should be emphasized that episcleritis is a disease of a collagenous tissue and not of a mucous membrane. No conjunctivitis was recorded for this patient. Mucous membrane involvement of the conjunctivas is seen more frequently in such conditions as Reiter's syndrome, Stevens-Johnson disease, Behçets disease and other related syndromes.

DR. REINHARD: We do not seem to be making much progress from this approach. Let us see if we can get help from another angle. Dr. Sherry, would you tell us what the present concept is, or at least your own present concept, regarding the relationship between rheumatoid arthritis, lupus, polyarteritis, polymyositis and dermatomyositis. What is the common denominator of these diseases? I know there is no specific answer to this question, but I wonder if you would just give us your own ideas about the problem.

DR. SOL SHERRY: There are, of course, certain similarities in this group of diseases which involve the connective tissue and blood vessels. In addition to producing overlapping clinical pictures, they characteristically present certain common pathologic findings, namely, the presence of "fibrinoid" scattered throughout the connective tissue of the body. However, these observations only suggest a common type of reaction pattern. Furthermore, the observation that similar "fibrinoid" lesions may be provoked in animals by foreign protein hypersensitivity experiments cannot be literally interpreted that this group of diseases all have a common type of etiology.

The studies of Klemperer and his group* in systemic lupus indicate that the "fibrinoid" in the latter disease probably represents proteinaceous material derived from nucleoprotein breakdown which is deposited in the ground substance of the connective tissue as well as in the hyaline thrombi of the glomerular tuft. In addition, in lupus the abundantly scattered hematoxylin bodies and the intracellularly phagocyted material characteristic of the L.E. cell are also composed of partially depolymerized desoxyribonucleoprotein. Finally, in lupus an abnormal circulating plasma globulin is present which is capable of producing the L.E. phenomenon with normal white cells. These observations suggest that lupus is a disease of disordered nucleoprotein metabolism related to the presence of an abnormally circulating protein, and that the end products of this disturbance are deposited in and around the blood vessels and probably transude into the ground substance of the connective tissue. On the other hand the "fibrinoid" of rheumatic fever, rheumatoid arthritis and polyarteritis is not of nucleoprotein origin nor is there any evidence

* KLEMPERER, P. The significance of the intermediate substance of the connective tissue in human disease. *Harvey Lect.*, 49: 100, 1954.

of the presence of hematoxylin bodies in these diseases. It is just as likely as not that detailed chemical analyses of the "fibrinoid" in these diseases will prove to be dissimilar. It might also be pointed out that in none of these collagen disorders has the fibrinoid been shown to contain hydroxyproline, an amino acid unique to collagen, suggesting, of course, that the fibrinoid is not derived from collagen and that the collagen may not be altered at all.

From these few observations I am of the opinion that although clinical and pathologic similarities may exist in this group of disorders which involve the blood vessels and connective tissue of the body, they are basically different diseases which do not interconvert but may exist together. It would also appear scientifically sound to keep an open mind about the etiology of each of these separate diseases rather than to accept a common denominator.

DR. REINHARD: Dr. Sherry, in view of the fact that it is necessary to make a specific diagnosis here, would you care to hazard a suggestion?

DR. SHERRY: I would guess that the patient had rheumatoid arthritis and, in addition, dermatomyositis.

DR. REINHARD: In considering the neurologic findings, you will recall that there was atrophy of the interosseus muscles, the wrist extensors and the foot extensors. The patient had wrist drop and foot drop bilaterally. Ankle jerks were absent and there was a diminished knee jerk on the left. There were diminished sensations of pain and light touch along the lateral aspects of the lower extremities, dorsum of the right foot and ulnar distribution of the right hand. Vibratory and position sense were diminished in both the hands and the feet. So there were sensory as well as motor changes. Dr. Levy, how would you interpret these findings?

DR. IRWIN LEVY: I think this is definite evidence of peripheral neuritis. The absent deep reflexes plus the combined motor and sensory deficits establish this diagnosis.

DR. REINHARD: Is this going to be of any help to us in trying to make a specific diagnosis, or is it a non-specific finding that can occur in any of the diseases we have been discussing?

DR. LEVY: It is a non-specific finding. Peripheral neuritis occurs most frequently in periarteritis, less frequently in dermatomyositis and least commonly in lupus.

DR. REINHARD: Dr. Lam, do you have any data on the relative incidence of this type of peripheral neuropathy in the various connective tissue diseases?

DR. ROBERT LAM: Peripheral neuropathy of the type we have been discussing is not infrequent in the collagen diseases, particularly in periarteritis. I believe that in the present case the peripheral neuropathy could certainly be a part of the basic disturbance. On the other hand, it could be an incidental finding. I believe one has to consider nutritional polyneuritis as well. In addition, there is evidence here of possible drug toxicity which can on occasion cause a peripheral neuropathy, such as has been reported following the administration of cortisone. I would like to point out that even though peripheral polyneuritis occurs rather frequently in collagen type diseases, the picture of polyneuritis in this case may be incidental and not related to the fundamental pathologic process.

DR. REINHARD: Do you have anything to add, Dr. Levy?

DR. LEVY: No. I would agree with Dr. Lam. It is interesting, however, that the neurologic picture apparently improved as the systemic disease improved, but whether one can infer from this that they were of similar etiology is conjectural.

DR. REINHARD: I would like to concentrate our attention on the drug history given by the patient. You remember that she received one injection of gold one and a half years prior to admission to Barnes Hospital. I assume we may disregard this as being of little significance. During the six months prior to admission to Barnes Hospital she had apparently received large amounts of antibiotics, including prolonged sulfonamide therapy. Dr. Alexander, do you think that the patient might have had polyarteritis? Could she have developed that variety of polyarteritis referred to as hypersensitivity angiitis superimposed upon her previous rheumatoid arthritis? Might this account for the terminal events in her illness?

DR. HARRY ALEXANDER: No, I do not believe so. To begin with, examination of the biopsy specimen showed a generalized polymyositis and some lesion in the arterioles. Polymyositis is uncommon with polyarteritis in which one usually finds areas of muscle necrosis surrounding the affected arterioles. Frequently, in polyarteritis, a biopsy specimen not secured at the site of a diseased vessel will reveal nothing abnormal. In the specimen described here both the muscle lesion and the arterial lesion appear.

The diagnosis of polymyositis was made but polyarteritis was evidently not considered so that the myositis and arteritis may be attributed to some other cause. It seems to me that the biopsy specimen is compatible and even typical of rheumatoid arthritis in which an arteritis occurs also.

DR. REINHARD: Dr. Luse, do you think we are safe in saying that the changes in the muscles were not due to polyarteritis and that we will have to assume there is another lesion present?

DR. LUSE: No, I do not believe we can say that. The changes in the muscle are certainly not diagnostic of polyarteritis but can occur in polyarteritis. These muscle changes are not incompatible with a diagnosis of polyarteritis.

DR. REINHARD: I think we should now consider some of the findings that this patient had in relation to the findings usually seen in disseminated lupus. The patient's blood pressure was normal; it is often high in lupus and in about 60 per cent of patients with polyarteritis. The blood pressure is usually normal in dermatomyositis. Fever may occur in all these conditions so this does not help us. Polyarthritis commonly occurs in disseminated lupus and, as Dr. Kingsland has pointed out, may be indistinguishable from rheumatoid arthritis. Joint swelling may be present in polyarteritis, but not as commonly as in lupus. It is my impression that in dermatomyositis one often sees joint involvement. The type of joint involvement that this patient had, however, with classic ulnar deviation and definite joint destruction, is extremely uncommon in uncomplicated dermatomyositis. We have already discussed the occurrence of polyneuritis which was a very prominent symptom in this patient. It was not due to nutritional factors. Polyneuritis is relatively rare in the collagen diseases, although one cannot escape the impression that it is more common in polyarteritis than in the others. Polymyositis has been described as occurring in all of these conditions, although, as Dr. Alexander has pointed out, the pathologic pictures may differ. The white count does not help a great deal here. The patient's white counts were in the high normal range. Leukopenia, of course, is a common but not universal finding in disseminated lupus. The white counts in polyarteritis are usually considerably higher than those observed in our patient. Leukocytosis is characteristic in dermatomyositis, but in perhaps a fourth of the patients the white counts are low or normal. The normal platelet count does not help us. Platelets may be depressed in lupus but are usually normal in the others. The anemia in this patient was very mild. Anemia is common in disseminated lupus, less common in polyarteritis. A very mild anemia may be present in the usual case of dermatomyositis or polymyositis.

We have not discussed the possibility of a renal lesion. The patient had six urinalyses carried out and of these, three showed no red cells and three showed microscopic hematuria, varying from a few to perhaps five or ten red cells per high field. As the patient was well beyond the menopausal stage, we may interpret this as representing inconstant hematuria. Renal involvement is common in disseminated lupus, is present in at least 40 per cent of cases of polyarteritis according to one series, and would not be a characteristic finding in dermatomyositis. The L.E. test is really helpful only if positive; a negative result does not rule out lupus and one may observe L.E. cells in a number of other lesions. Dr. Moore would you like to give us your opinion as to which of these entities, if any, the patient most likely had?

DR. CARL MOORE: I do not believe I can improve on Dr. Sherry's interpretation that the lesion is probably a combination of rheumatoid arthritis and dermatomyositis.

DR. REINHARD: We now have only one other thing to discuss briefly. Dr. Massie, how would you interpret the patient's sudden and unexpected death?

DR. EDWARD MASSIE: Since we are thinking in terms of collagen disease, one would consider three possible lesions: myocarditis, pericarditis and endocarditis. The patient did not seem to have any of these conditions clinically. Therefore, I would assume that the type of death would be in favor of a coronary thrombosis. One electrocardiogram was taken two weeks prior to death. This electrocardiogram was distinctly abnormal but did not show evidence of infarction. It showed inversion of the T-waves in six of twelve leads with the greatest abnormality in leads II, III and aVF. I would suspect that ischemia of the diaphragmatic portion of the posterior wall was definitely present. The electrocardiographic findings may also be compatible with a diagnosis of pericarditis or myocarditis. In view of the manner in which she died, however, I would favor coronary artery disease with a terminal infarction. Coronary

thrombosis is a very rare complication of lupus erythematosis. In fact, none of the thirty-eight patients studied by Harvey and his associates had evidence of such a lesion. Coronary thrombosis is much more likely to occur in periarteritis.

DR. REINHARD: If the coronary thrombosis was related to the primary underlying disease, you would believe that this is, at least, some evidence in favor of polyarteritis rather than dermatomyositis or lupus?

DR. MASSIE: Yes.

DR. REINHARD: That was also my impression. The house staff diagnoses were rheumatoid arthritis, myositis due to rheumatoid arthritis, acute multiple neuritis, infarction of the myocardium due to arteriosclerosis, and fibrosis of the lung following tuberculosis. My own belief is that the patient, as Dr. Sherry has suggested, had two diseases: rheumatoid arthritis plus one of the other connective tissue diseases we have discussed. I must confess that I am attracted by the possibility that the patient might have had rheumatoid arthritis for a period of two years. Sometime within the last two to six months polyarteritis probably developed, and I am putting this down for my first diagnosis. Polyarteritis could account for the polyneuritis and polymyositis. It could account for the renal lesion. It would be the best explanation for the terminal myocardial infarction, which I believe the patient had. Another distinct possibility, which we cannot possibly rule out, is that the patient had disseminated lupus throughout her entire illness and that the arthritis was a rheumatoid-like arthritis, such as is seen in lupus. A third possibility is that the patient had dermatomyositis or neuromyositis, if you wish to use that term. Dermatomyositis, however, would not account for the arthritis, although you certainly get much involvement of the joints in this disease. I believe, as Dr. Sherry has suggested, that if the patient did have dermatomyositis, one would have to postulate that she also had rheumatoid arthritis. I am inclined to put the diagnosis of dermatomyositis way down on my list, primarily because of the myocardial infarction and because I believe that peripheral neuritis is more common in polyarteritis than in dermatomyositis. I think it should be emphasized that the data do not permit us to make a positive diagnosis.

PATHOLOGIC DISCUSSION

DR. ROBERT C. AHLVIN: The external examination of the body of this middle-aged woman revealed marked muscle atrophy and joint deformities that were described previously. The left knee was opened. The articular surfaces were smooth and glistening, and grossly the joint appeared normal. The joints in the hands could not be examined.

Examination of the viscera revealed obliteration of the pericardial cavity by fibrinous adhesions. The pericardial sac was easily separated from the heart, leaving the epicardial surface covered by a thick shaggy layer of fibrin. On culture this pericardial exudate proved to be sterile. There was only moderate arteriosclerosis of the coronary arteries. However, in the right coronary artery as it approached the posterior longitudinal sulcus there was an abrupt change in the character of the wall. For a distance of 1 cm. the wall of the artery was markedly thickened, and in this area the vessel contained a thrombus. In the myocardium of the posterior wall of the left ventricle and of the posterior part of the interventricular septum there was an irregular yellow area surrounded by congestion which we interpreted as an acute myocardial infarct. The character of this artery prompted a rather close inspection of the valves. The outer third of the leaflets of the mitral valve was somewhat thickened, and a few of the chordae tendineae were thickened. In two areas there were small granular projections from the atrial surface of the valve. These were friable, and none was found on the ventricular surface of the valve. The leaflets of the tricuspid valve were also slightly thickened, but the endocardial surface of this valve was smooth. One of the chordae tendineae was thickened. The heart was hypertrophied slightly, weighing 330 gm. The lungs were congested and slightly edematous. There was moderate focal atelectasis. The liver was congested. The kidneys were of normal size and contained a few small superficial scars. No other abnormalities were noted in the viscera.

DR. MARGARET G. SMITH: The significant gross findings, in addition to atrophy of the muscle and deformities of the joints, were limited to the heart. The microscopic changes were more widespread. In the sheath of the tendon of the semitendinosus muscle there was a sharply outlined microscopic lesion having the characteristics of a rheumatoid nodule. (Fig. 1.)

The section taken from the knee joint showed very little. Dr. Ahlvin has told you that we were unable to examine the joints which showed the greatest deformities. In the knee joint there was

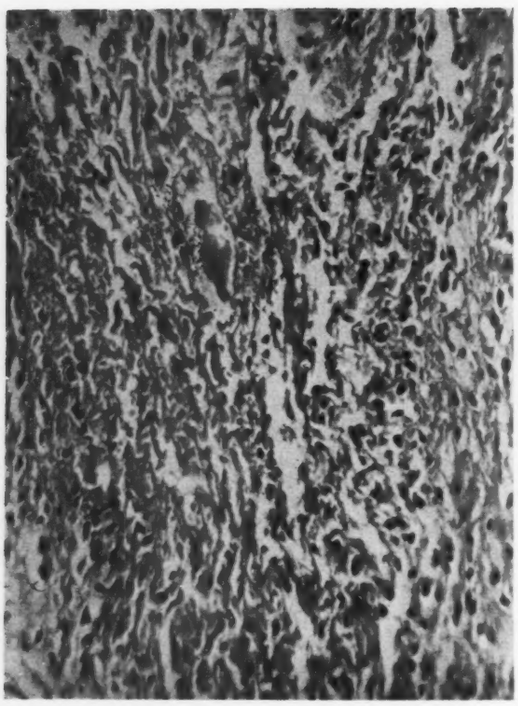

FIG. 1. Wratten B & G filters were used in taking this photomicrograph and all the following illustrations. Rheumatoid nodule in tendon sheath showing central necrosis and palisading of marginal cells; hematoxylin and eosin stain, × 100 (approximate).

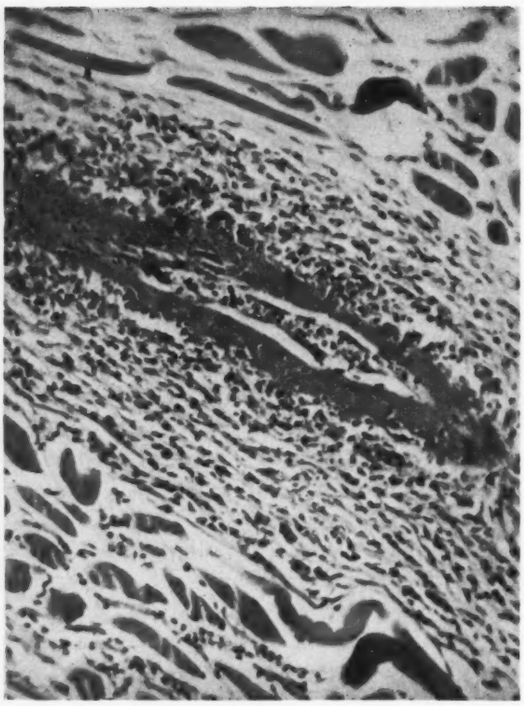

FIG. 2. Small artery in muscle showing necrosis of the entire wall and cellular infiltration of the adventitia; hematoxylin and eosin stain, × 100 (approximate).

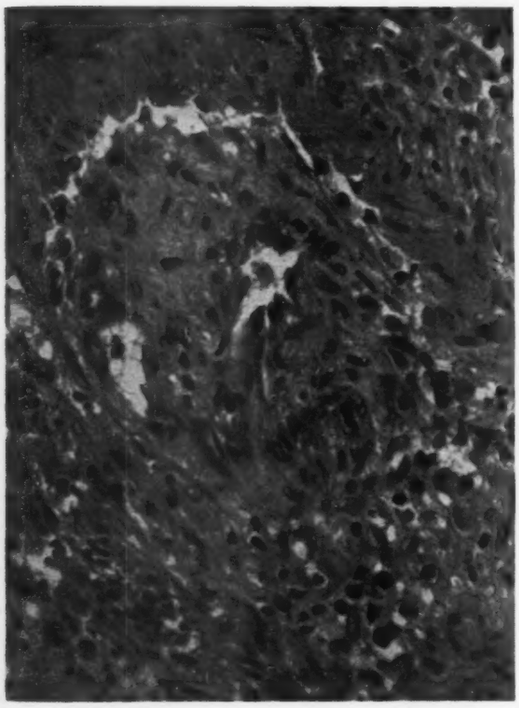

FIG. 3. Small artery containing a recanalized thrombus. At the lower right, the wall of the artery is replaced by cellular connective tissue; at the lower left, the media is infiltrated with mononuclear cells; hematoxylin and eosin stain, × 250 (approximate).

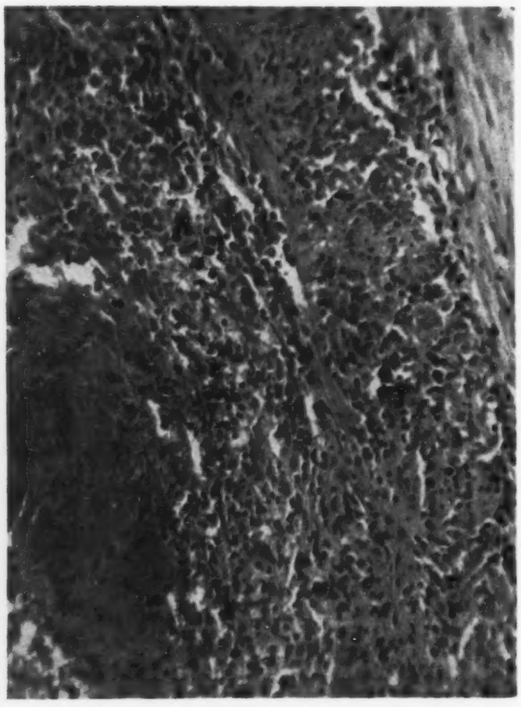

FIG. 4. Small artery showing mononuclear infiltration of the media and proliferation of fibroblasts and mononuclear infiltration in the intima. At the lower left fibrinoid necrosis of the intima is seen; hematoxylin and eosin stain, × 100 (approximate).

FIG. 5. Wall of the coronary artery showing necrosis of the media and adventitia, fibrous intimal proliferation and, at top of the photomicrograph, a recent thrombus; hematoxylin and eosin stain, × 100 (approximate).

FIG. 6. Coronary artery showing necrosis of the media and adventitia at the left, fragmentation of the internal elastic membrane and, at the upper right, a recent thrombus; Verhoeff-Van Gieson stain, × 100 (approximate).

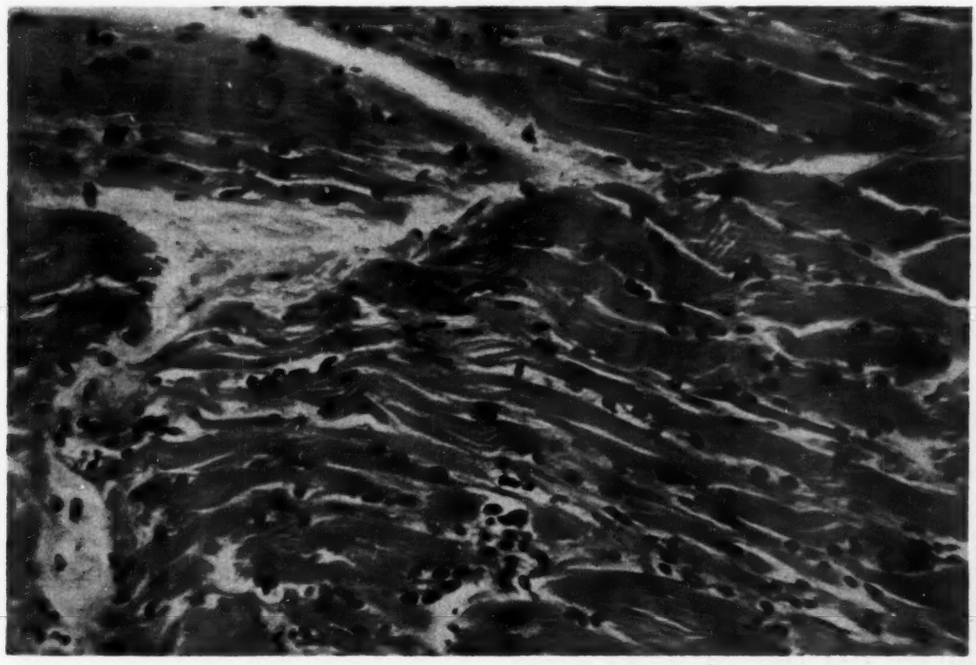

FIG. 7. Myositis with mononuclear infiltrate between muscle fibers; hematoxylin and eosin stain, × 200 (approximate).

only a slight non-specific chronic inflammation in the synovial tissue at the perichondrial margin. No pannus formation was present.

Polyarteritis involved the right coronary artery, many small arteries of the muscles and nerves, and a few small arteries of the heart, liver, kidneys, intestinal wall, thyroid, breast and periadrenal tissue. With the exception of the coronary artery, the arteries affected were less than 1 mm. in diameter. The arterial lesions varied in age and in the extent to which the vessel wall was damaged. There was complete necrosis of the wall of a few small arteries. Such a small artery observed in a section of muscle is shown in Figure 2. Surrounding this vessel was an infiltrate of mononuclear cells and polymorphonuclear leukocytes, including a few eosinophilic leukocytes. Another small artery, also from muscle, is shown in Figure 3. An organized thrombus filled the lumen. There was proliferation of fibrous tissue and an infiltrate of mononuclear cells in the adventitia. The intima was thickened and a part of the media of the vessel was replaced by fibrous tissue. The media adjacent to the defect was infiltrated with mononuclear cells. In other arteries there was a mononuclear infiltrate throughout the media and a proliferation of fibroblasts and mononuclear infiltration in the intima. Fibrinoid necrosis in the proliferating tissue of the intima was present in some of these vessels (Fig. 4) and recent thrombi occluded the lumina of others.

The wall of the right coronary artery showed both chronic inflammatory and acute inflammatory reaction with necrosis. There was fibrous intimal thickening and in the adventitia, an infiltrate of lymphocytes, large mononuclear cells and plasma cells. There was also necrosis of the adventitia and media involving a part of the circumference of the artery. The extent of the necrosis varied in sections taken at different levels of the artery. In and about the areas of necrosis there were polymorphonuclear leukocytes and fragmented cells. A recent thrombus occluded the vessel. (Figs. 5 and 6.) Aneurysms of the damaged vessels did not occur, and the only infarct resulting from occlusions of arteries was in the heart.

Myositis like that observed in the biopsy specimen was present to some extent in all the muscles microscopically, but was variable in degree. (Fig. 7.) There was an infiltrate of mononuclear cells between muscle fibers. A few muscle fibers were atrophied and stained deeply with eosin.

DR. REINHARD: Dr. Smith, how often do you see this sort of change in the muscle in association with polyarteritis? Would you comment on this? Is it very rare?

DR. SMITH: In my experience, in polyarteritis nodosa there have been changes as diffuse as this in muscles in which the vessels were also involved.

DR. ALEXANDER: It is compatible with rheumatoid arthritis?

DR. SMITH: I think it is compatible with the vascular changes which occur in association with rheumatoid arthritis or with polyarteritis nodosa.

In several sections of nerves some of the myelin sheaths are swollen, and in an occasional sheath there are droplets of fat which stain with Oil Red O.

In addition to the acute infarct of the myocardium there is a slight focal interstitial infiltrate of mononuclear cells. There are no lesions characteristic of rheumatic fever in either the myocardium or endocardium. There is an increase of fibrous tissue in the slightly thickened mitral valve, and the valve leaflet is vascularized. An infiltrate of mononuclear cells and proliferation of fibroblasts occurs in focal areas of the endocardium of the mitral valve and of the left ventricle. A slight fibrinoid change is also present in the connective tissue of the valve. The fibrinous pericarditis is partially organized and does not appear to be related to the infarct.

In general, the character of the polyarteritis in this case corresponds with that described in association with rheumatoid arthritis,* but there are some features having more resemblance to polyarteritis nodosa. With the exception of the coronary artery only the very small arteries are involved, as in the angiitis of rheumatoid arthritis. Although the arterial lesions are most numerous in muscles and nerves, small arteries of the liver, kidney, intestines and other sites are also involved. The latter distribution is more characteristic of polyarteritis nodosa than of the arteritis of rheumatoid arthritis. Thrombi, organized or recent, are present in a considerable number of vessels. These have been observed rarely with the arteritis in rheumatoid

* CRUICKSHANK, B. The arteritis of rheumatoid arthritis. *Ann. Rheumat. Dis.*, 13: 136, 1954; SOKOLOFF, L., WILENS, S. L. and BUNIM, J. J. Arteritis of striated muscle in rheumatoid arthritis. *Am. J. Path.*, 27: 635, 1949.

arthritis. Unlike the classic cases of polyarteritis nodosa, no aneurysms and no infarcts, with the exception of that in the myocardium, are present.

Final Anatomic Diagnoses: Rheumatoid arthritis; atrophy of the muscles of the thighs, legs, shoulders, arm and hands; polyarteritis with involvement of the right coronary artery, small arteries of the heart, muscles and peripheral nerves and a few small arteries of the abdominal organs, thyroid and breast; myositis; focal degeneration of myelin of peripheral nerves; endocarditis involving the mitral and tricuspid valves and the endocardium of the left ventricle; partially organized fibrinous pericarditis; hypertrophy and dilatation of the heart (380 gm.); recent thrombus occluding the right coronary artery at the site of arteritis; recent infarcts of the myocardium of the posterior wall of the left ventricle and the posterior part of the interventricular septum.

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Case Report

Isolated Congenital Bicuspid Pulmonary Valve*

Clinical and Pathologic Study

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THE purpose of this report is to present a case of isolated bicuspid pulmonary valve with pulmonary valvular insufficiency which was suspected clinically, diagnosed by cardiac catheterization and confirmed by autopsy. Although rare, this lesion presents a characteristic picture; ultimately it may be treated surgically. For this reason the unusually complete clinical material available in this case will be presented in detail.

CASE REPORT

A forty-three year old white housewife (University Hospitals Case No. 293-973) was admitted to University Hospitals of Cleveland for the second time on April 13, 1954 for cardiac evaluation.

At birth the patient had appeared normal but at the age of seven a diagnosis of "leakage of the heart" was made. She had no definite cardiovascular symptoms. At the age of thirty-four, during admission to a local hospital for lysis of pelvic adhesions, she was found to have a "to-and-fro" murmur at the base of the heart. On May 7, 1950, she was first admitted to University Hospitals because of pain and swelling of the right knee and ankle and chronic cough and weight loss. A diagnosis of advanced pulmonary tuberculosis, active and open, was made on the basis of chest x-rays and positive acid-fast sputum smears. Examination of the chest during this admission showed a blowing systolic murmur and a very loud and rough diastolic thrill in the third left intercostal space. Cardiothoracic ratio by x-ray was 13.5:26 and the pulmonary conus and arteries were prominent. An electrocardiogram showed right atrial hypertrophy (prominent P waves in Leads II, III, aV_R, and V_1) and probable right ventricular hypertrophy. Four blood cultures revealed no growth. The patient was transferred to Sunny Acres Tuberculosis Hospital where she was treated for seven months with streptomycin and para-amino salicylic acid. Pneumoperitoneum was induced in the third month. After the ninth month cultures gave negative results for tubercle bacilli. X-rays showed development of linear fibrosis in both lungs. (Figs. 1 and 2.) Vital capacity was 1.95 liters (65 per cent of normal) and maximum breathing capacity 54 liters per minute (51 per cent of normal).

In February, 1954, at which time the pulmonary tuberculosis was inactive and the patient was in full employment, she began to note dyspnea after pneumoperitoneum refill. Chest fluoroscopy showed hilar dance, and the diagnosis of pulmonary insufficiency was first suspected. In April she developed increased dyspnea, ankle edema and right upper quadrant tenderness attributed to liver engorgement. Diuresis followed bed rest and the administration of digitalis and mercuhydrin,® and the patient was admitted to University Hospitals for study.

On physical examination the patient did not appear ill. Her temperature was 37°C. and the pulse was 80 with frequent premature beats. The respiratory rate was 20 and the blood pressure 108/78 mm. Hg. The heart was not enlarged to percussion. There was visible and

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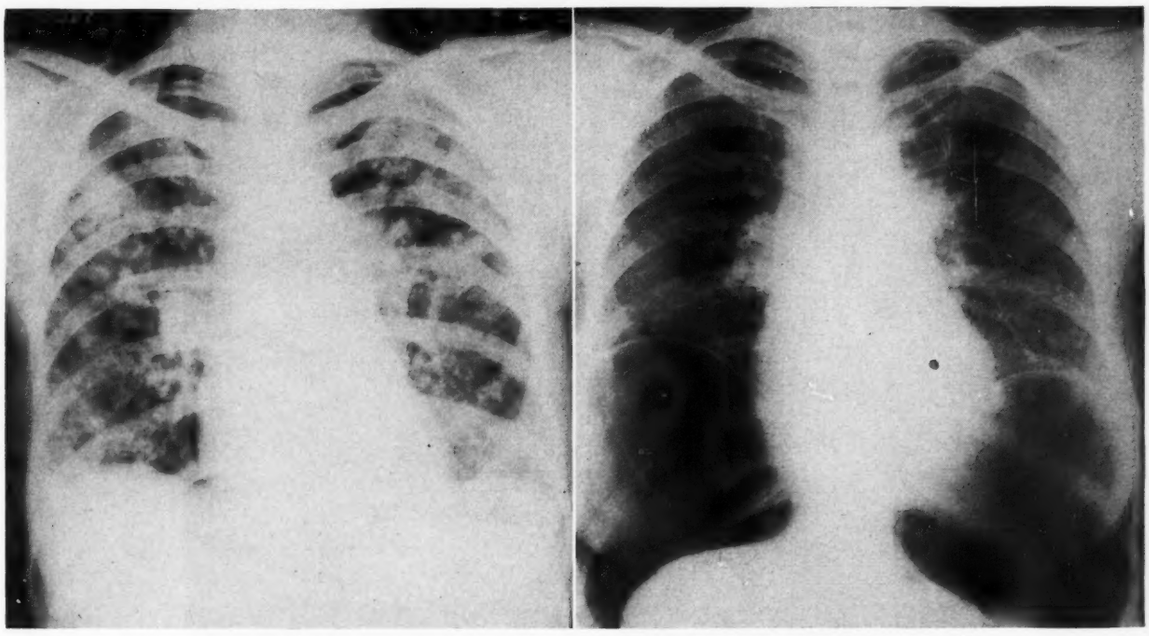

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FIG. 1. Chest roentgenogram (April 21, 1950) showing diffuse bilateral pulmonary infiltration.

FIG. 2. Chest roentgenogram (October 23, 1953) showing pulmonary fibrosis and pneumoperitoneum.

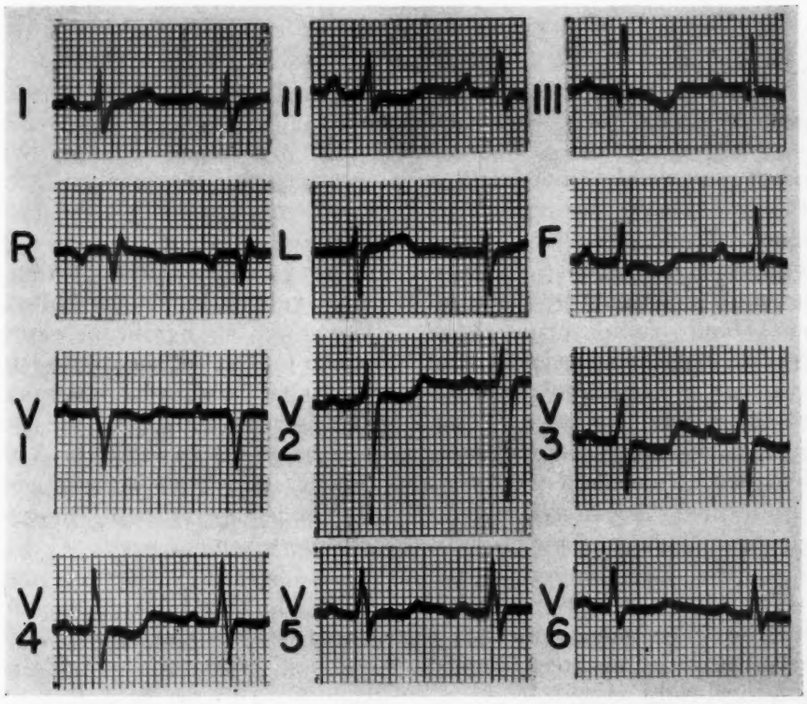

FIG. 3. Electrocardiogram (April 21, 1954) showing right atrial and probable right ventricular hypertrophy, digitalis and possible quinidine effect.

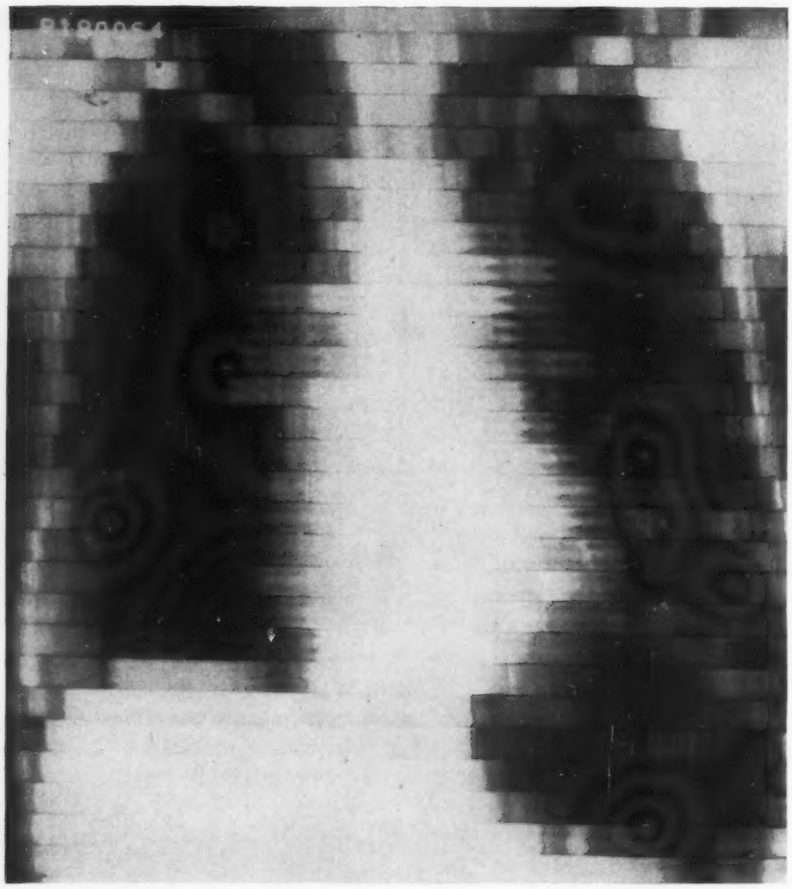

FIG. 4. Roentgenkymogram (April 21, 1954) showing increased pulsation of pulmonary conus and pulmonary arteries.

palpable increase of precordial activity, and a systolic thrill was palpable in the pulmonary area. The pulmonary second sound was absent, and a rough, grade III, decrescendo diastolic murmur was heard in the same area accompanied by an equally loud systolic murmur. Both murmurs were transmitted along the left sternal border and to the apex. No enlargement of the liver and no ankle edema were present.

Laboratory studies revealed the leukocyte count to be 7,000 per cu. mm. and the differential count to be normal. Hematocrit was 53 per cent, hemoglobin 16.0 gm. and the erythrocyte count 5.6 million. Examination of the urine gave normal results. Venous pressure was 62 mm. of saline. Arm-to-tongue circulation time (magnesium sulfate) was seventeen seconds and arm-to-lung (ether) eight seconds.

Electrocardiograms (Fig. 3) were unchanged from the record of the previous admission except for the appearance of ST-T changes due to digitalis and frequent unifocal ventricular and occasional nodal premature beats. These premature beats subsided after institution of oral quinidine sulfate.

X-rays and fluoroscopy showed hilar dance with wide pulsation in both mid-lung fields. There was no significant cardiac enlargement except for that of the outflow tract of the right ventricle. A roentgenkymogram (Fig. 4) showed increased pulsations of the pulmonary conus and the pulmonary arteries. A phonocardiogram (Fig. 5) showed a systolic murmur and an early diamond-shaped diastolic murmur in the second left interspace.

Cardiac catheterization was performed on April 20. The data are presented in Table I. There was no evidence of a left-to-right shunt. The rise of femoral artery oxygen saturation from 90 to 97 per cent after breathing oxygen indicated that there was no significant right-to-left shunt. Systolic pressure in the pulmonary artery was at the upper limits of normal. The cardiac output, estimated by the Fick principle,

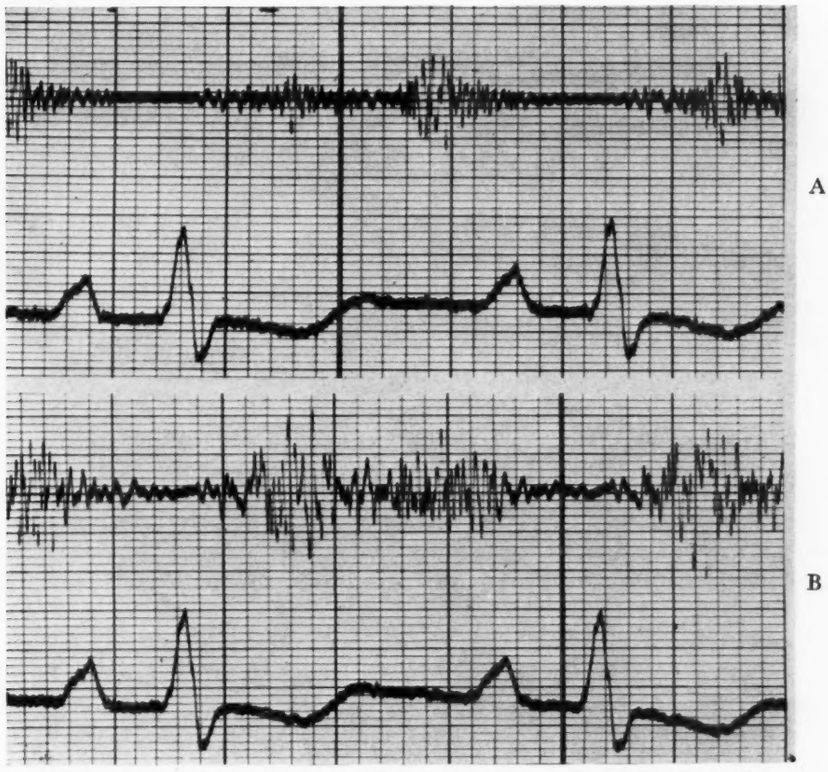

FIG. 5. Phonocardiogram (April 23, 1954). A, diaphragm, second left intercostal space; B, bell, second left intercostal space. Electrocardiogram. Lead II in lower half of each record; both records show a decrescendo diastolic murmur which is more prominent in B, and both show a systolic murmur.

was 3.2 liters per minute, and the cardiac index 2.1 liters per square meter per minute. The shape of the pulmonary artery pressure curve, which was uniform in both right and left branches and in the main pulmonary artery, was characteristic of pulmonary valvular insufficiency (see subsequent discussion).

The catheterization was uneventful except for the appearance of occasional ventricular premature beats while the catheter was being manipulated in the right ventricle. Because the patient was then without symptoms, possible surgical measures were not thought advisable and the patient was discharged on April 22, 1954.

On the following day at her place of employment she suffered a brief syncopal attack during which her pulse was at first unobtainable and then temporarily irregular. She appeared to recover from this without ill effect but the next morning she was found dead in her room. There was no circumstantial evidence of convulsion or other events during the terminal period, and rigor mortis was present.

Report of Autopsy (*No. 12972*). The body weighed 50 kg. and measured 168 cm. in length. There were numerous petechiae, some confluent, and marked cyanosis of the upper part of the body.

The heart weighed 365 gm. The pericardium was normal, containing 100 cc. of clear yellow fluid. The right atrium was slightly dilated. The right ventricle was markedly dilated, and the wall measured 0.5 cm. in thickness. The columnae carneae and papillary muscles of the right ventricle were greatly enlarged. No evidence of trauma produced by cardiac catheterization was noted. The left atrium and ventricle were not unusual.

The pulmonary valve measured 9 cm. in circumference and did not appear stenotic. There were only two cusps. (Fig. 6.) The commissures were anterior and posterior. The cusps were separated from each other at each commissure by a gap 0.5 cm. wide. The right cusp was thin and shortened throughout, not exceeding 0.8 cm. in height and averaging 0.5 cm. in height. The free margin of this cusp was slightly thickened with a smooth endocardial surface. The cusp was

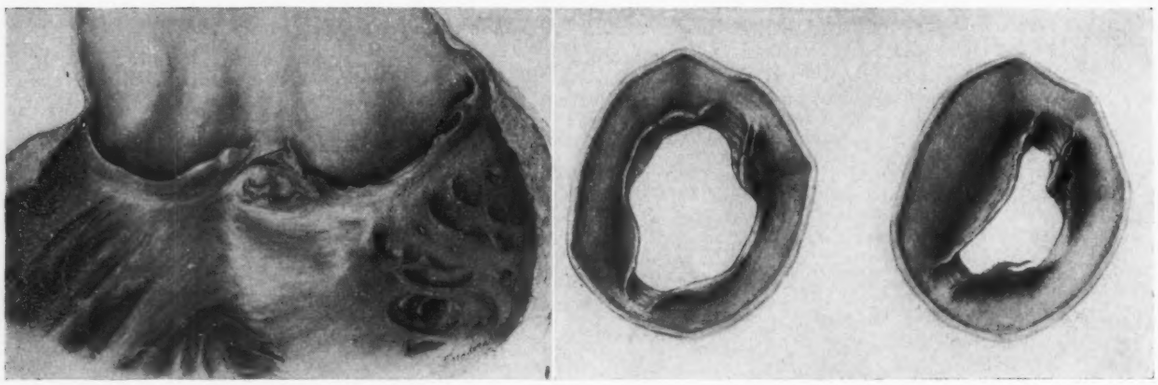

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FIG. 6. Drawing of pulmonary valve opened; left cusp on the right; note sac in center between cusps. (See text.)

FIG. 7. Drawings of pulmonary valve from above; cusps in open (left) and closed (right) positions; left cusp on the right.

soft and pliable. Neither a ridge nor a fibrous band was present in either right or left pulmonary cusp.

The anterior and posterior margins of the left cusp extended toward each other in the line of the commissural attachments. Approximately 1.0 cm. from each commissure they terminated in ragged projections. The cusp was continued between these portions, closer to its attachment, as an irregular fringe that varied from 0 to 0.5 cm. in height. The fragments of the left cusp were thin, soft and pliable, and the free margins were thin. The endocardium covering the cusp was smooth and glistening. The valves were anatomically incompetent. (Fig. 7.) No vegetations were present. Twelve millimeters directly below the deficient mid-portion of the left cusp there was an area of thickening of the endocardium measuring 4 to 6 mm.

Immediately below the posterior commissure there was a smooth elevation of the endocardium which measured 0.5 cm. in vertical diameter, 0.3 cm. in width and 0.2 cm. in thickness. The upper end was 0.5 cm. below the attachment of the right and left pulmonary cusps at the commissure. There was an opening on the left side of the elevation, 0.3 cm. in greatest diameter. Section of the elevation showed it to be a thin-walled sac containing blood. (Fig. 8.)

The tricuspid, mitral and aortic valves were

TABLE 1
DATA OF CATHETERIZATION

Location	Pressure (mm. Hg)		Oxygen Content (cc./100 cc. blood)
	Range	Average	
Left pulmonary artery	25–32/3–6	29.5/5.2 (11)	12.3
Right pulmonary artery	same	same	12.3
Right ventricle	27–35/3–7	29.6/5.3 (11)	12.3
Right atrium: low	2–8/–2–4	6/0 (2)	12.4
Right atrium: mid	same	same	12.3
Femoral artery	105–115/60–67	111/64 (78)	17.9 (90% saturated)*
			19.5 (97% saturated)†

* Breathing air.
† Breathing 100% oxygen.

FIG. 8. Vertical section through sac in posterior pulmonary commissure; sac is in left center of section (elastic tissue Van Gieson's stain, × 6.5).

not unusual and measured 12.5 cm., 10.0 cm. and 6.0 cm. in circumference, respectively. There was no communication between the right and left heart chambers. The foramen ovale was closed. The ductus arteriosus was represented by a thick, firm cord.

The right coronary artery was predominant. There was slight coronary arteriosclerosis. The aorta measured 6.0 cm. in circumference at the base and was not unusual. The pulmonary artery measured 9.0 cm. in circumference, and the main branches were dilated. Their walls were thin, soft and elastic and the intima was smooth and glistening.

Fibrous adhesions of the pleura were present over both lungs. The lungs showed firm and subcrepitant portions of all lobes. The cut surfaces were coarsely spongy with scattered emphysematous foci throughout. In the right lung there were a few round foci varying from 0.2 to 0.4 cm. in diameter, which were of friable calcific material. The larynx, trachea, right main bronchus and right lower lobe bronchus were partly filled by fluid and food particles. The mucosal surfaces were red.

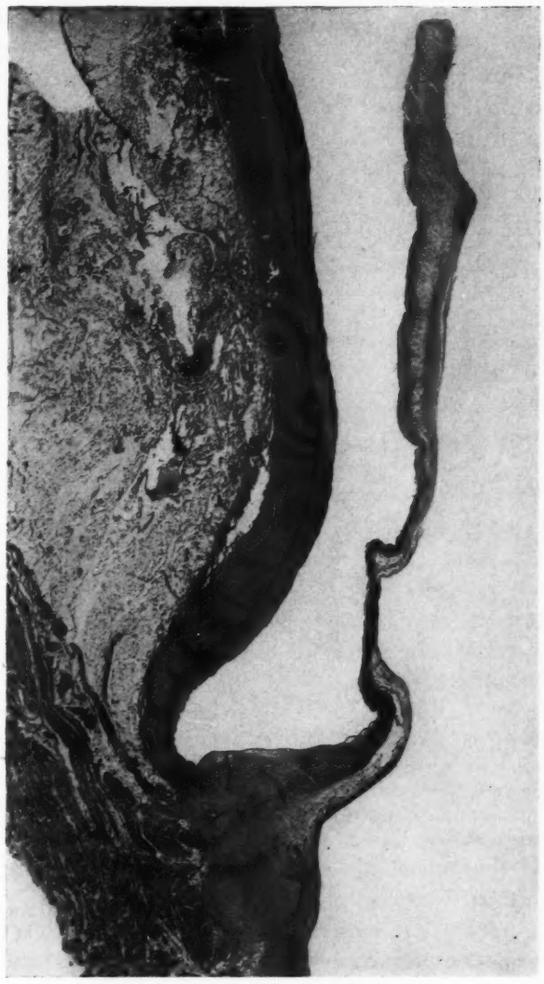

FIG. 9. Vertical section through center of an aortic cusp (hematoxylin and eosin stain, × 6.5).

Microscopic findings: The structure of an aortic cusp and of the right pulmonary cusp is illustrated in Figures 9 and 10. Each section is from the center of the cusp and is reproduced at the same magnification. Except for their size and irregularity, the pulmonary cusps were not unusual. The roof of the small endocardial sac below the posterior pulmonary commissure also consisted of fibro-elastic tissue and was covered on both sides by endothelium. (Fig. 8.) Sections of the pulmonary artery and aorta showed no abnormality.

The small nodules of the right lung consisted of fibrous tissue with central caseous necrosis. Acid-fast staining showed no tubercle bacilli. Pulmonary interstitial fibrosis and vesicular emphysema were present. The small pulmonary vessels were dilated and thin-walled.

The main pathologic diagnoses made from the

FIG. 10. Vertical section through center of right pulmonary cusp (hematoxylin and eosin stain, original magnification × 6.5).

autopsy were isolated congenital bicuspid pulmonary valve, with hypoplasia of the pulmonary cusps producing pulmonary valvular regurgitation and hypertrophy and dilatation of the right ventricle. Healed pulmonary tuberculosis with secondary pulmonary fibrosis and emphysema was also revealed.

COMMENTS

This case may be considered from two major aspects: (1) as an example of the rare congenital lesion of isolated bicuspid pulmonary valve and (2) as a thoroughly studied case of pulmonary insufficiency.

Bicuspid Pulmonary Valve. Incidence: Isolated bicuspid pulmonary valve is extremely rare, although the pulmonary valve is frequently found to have two cusps in the heart which has more serious congenital anomalies.

The incidence of bicuspid pulmonary valve in Abbott's series of 1,000 cases of congenital heart disease was 3.1 per cent.[1,2] In routine autopsies the incidence is 0.052 per cent, as compared with an incidence of 0.154 per cent for bicuspid aortic valves.[3]

Bicuspid pulmonary valve is usually found as part of a major congenital anomaly. Koletsky states that one third of the cases are associated with tetralogy of Fallot.[3] In another series of bicuspid pulmonary valves sixty-two of sixty-four cases had interventricular septal defect, pulmonary stenosis or both, and one had bicuspid aortic valve, thus leaving only one case of isolated bicuspid pulmonary valve.[4] Among Abbott's thirty-one cases, only one had bicuspid pulmonary valve as the primary defect.

Pathogenesis: Bicuspid pulmonary valve is usually considered to be congenital. In one case the third valve became fused to the wall of the artery by arteritis resulting from pressure of an aortic aneurysm.[5] (Case 4, Table II.) This is the only case the authors have encountered of obviously acquired bicuspid pulmonary valve.

The valvular deformity in the present case is considered to be congenital because, except for small size and irregularity, the microscopic structure of each cusp was not abnormal. Syphilis is excluded because there was no aortic involvement, no stigma of inflammatory disease of the pulmonary artery and no scarring or vascularization of the pulmonary valve commissures.

Rheumatic disease may be excluded as the cause of the valve deformity. There was no thickening or fibro-elastic reduplication of the ventricularis layer of the pulmonary cusps. Moreover, no vascularization of the free part or base of the cusps was found, and there was no inflammatory exudate of the cusps. Stigmata of rheumatic disease were not found elsewhere in the heart.

The possibility that shortening of the cusps was the end result of subacute bacterial endocarditis, superimposed on a congenital bicuspid valve, was considered. Because of absence of scarring or other evidence of remote inflammation of the cusps, this possibility was considered most unlikely, although it could not be absolutely excluded.

It is therefore probable that the present bicuspid valve was congenital in origin. Koletsky describes three types of congenital bicuspid pulmonary valve: (1) two normal cusps, (2) one cusp subdivided by a congenital ridge and (3) one cusp containing a small fibrous band in the bottom of the sinus of Valsalva. The present case does not fit any of the three types, since the valves were not normal and since neither congenital ridge nor fibrous tissue was noted. It also

differed by the presence of a sac below the posterior pulmonary commissure. It is possible that the endocardial sac was a rudimentary cusp and represented a failure of growth of one of the three endocardial pouches formed in the development of the pulmonary valve. The sac was situated below the level of commissural attachment of the cusps but its lower margin was approximately at the level of attachment of the mid-portions of the two cusps. If the sac were actually an endocardial pocket and were produced by the action of the regurgitant stream of blood impinging on the endocardium below the commissural separation, it might be expected that the sac would open above and not on the left side. Examined microscopically, the sac resembled a cusp more closely than an endocardial pocket. Only a few elastic fibers of the endocardium around the lower attachment of the sac were continued across the base of the attachment. In typical endocardial pockets the elastic lamellae of the pockets are continuous with the contiguous endocardium.[6,7] In the present case the fibrous adhesion of the free edge of a rudimentary cusp to the lower portion of the pulmonary artery may explain the conversion of a cusp into a sac. (Fig. 8.)

Koletsky has stated that a congenital bicuspid valve may arise before the division of the truncus arteriosus into pulmonary artery and aorta (1) by the formation of only three endocardial swellings of the truncus instead of four, (2) by faulty growth or the position of the dividing septum or (3) by fusion of two halves of the lateral swelling at the time of septation. After division of the truncus, the anomaly may arise (1) by an abnormality of the hollowing-out process of the endocardial pads, (2) by fusion of two cusps or (3) possibly by disappearance of one cusp. If one assumes the sac to be a deformed left cusp, the last explanation would account for the present case.

Previously reported cases of isolated bicuspid pulmonary valve: The earliest case of isolated bicuspid valve was reported by Petsche[8] in 1736. The complete report states: "In another male cadaver the pulmonary artery was furnished with only two valves; these were larger than usual." This case is not included in the tabulation because so little information is given.

In Table II are presented sixteen cases of isolated bicuspid pulmonary valve collected from the literature, including the present case. Nine were male, six female and one was not specified. As already noted, the condition was definitely acquired in Case 4 alone, while in the rest it appears to have been congenital in origin.

The cause of death is indicated in fifteen cases. In nine the cause of death is not related to the cardiac anomaly. Four patients died of congestive heart failure and one of bacterial endocarditis. The cause of death in the present case is unknown but may have been a cardiac arrhythmia. The observations at autopsy of acute passive hyperemia of the lungs, liver and spleen are consistent with acute congestive heart failure. The presence of gastric contents within the upper respiratory tract and right lung bronchi, without acute inflammation, is thought to indicate terminal aspiration of vomitus that may have produced marked anoxia. There were no vascular thrombi or emboli within the heart or elsewhere, and the central nervous system showed no abnormality. There was no evidence to associate the patient's death with the cardiac catheterization performed four days previously. The development of ventricular premature beats prior to the last hospital admission may have presaged terminal ventricular fibrillation. This case therefore probably belongs with the five others in which death occurred from cardiovascular disorders, although not as a direct result of the anomaly. The average age of death in this series is 43.9 years and ranges from ten to seventy-five years. Thus isolated bicuspid pulmonary valve has a relatively good prognosis and is seldom a primary cause of death.

Associated heart disease was definitely present in three and probably present in two of the sixteen cases. Cases 3 and 11 had rheumatic heart disease, and Case 2 definitely had bacterial endocarditis. The multiple aortic aneurysms in Case 4 may represent luetic aortitis, while the "lymph" and thickened valves in Case 1 probably indicate bacterial endocarditis. The incidence of probable bacterial endocarditis in this series is 12 per cent, which may be compared with the incidence of 16 per cent in fifty cases of bicuspid aortic valve.[18] There is only one case in the present series with definite rheumatic involvement of the pulmonary valve. In contrast Koletsky states that most bicuspid aortic valves in adults are acquired lesions produced by rheumatic fever, a conclusion based on careful microscopic study.[19] In the absence of such studies, the true incidence of rheumatic heart disease is uncertain in the present series.

Clinical symptoms are reported in eleven

TABLE II

CASES OF ISOLATED BICUSPID PULMONARY VALVE

Author, Date and Case No.	Age and Sex	Pathologic Findings	Cause of Death	Cardiac Symptoms	Signs	Comments
Graves,[9] 1843 Case 1	66, M	Two pulmonary valves, both coated with recent deposition of lymph, valves thickened and opaque; emphysema	Pneumonia	None described	No cardiac signs described	.....
Paget,[10] 1844 Case 2	20, F	Hypertrophy, right auricle and ventricle; bicuspid pulmonary valve, cusps thickened and opaque; pulmonary artery thrombosis	Bacterial endocarditis	Cough, anasarca, palpitation, fainting, fits	Loud bellows [systolic], murmur accompanied and terminated first sound at base, wide radiation	.....
Grawitz,[5] 1887 Case 3	31, M	Aortic aneurysm; insufficiency aortic valve, thickening mitral; two pulmonary cusps normal size and position; area of third (overlying aneurysm) smooth endothelium, no trace of cusp	Heart failure	Congestive heart failure	Loud diastolic murmur over pulmonary artery; systolic and diastolic murmurs in aortic area; systolic murmur at apex	History of rheumatic fever
Grawitz,[5] 1887 Case 4	46, M	Heart hypertrophied; multiple aneurysms aortic arch; two normal pulmonary cusps, third adherent to wall adjacent to aneurysm and incompetent	Heart failure	Congestive heart failure	Heart enlarged to right; loud precordial systolic murmur; no diastolic described	Condition probably acquired
Stintzing,[11] 1889 Case 5	64, F	Heart 670 gm.; right ventricle dilated and hypertrophied; one pulmonary cusp missing, in its place partly clear endocardium, partly rudimentary valve; mild emphysema	Heart failure	Vague symptoms, including dyspnea; congestive heart failure	Pulse became irregular; heart enlarged to right and left; diastolic murmur third and fourth left interspace, transmitted to apex and carotid; signs of emphysema and bronchitis	.....
Simpson,[12] 1898 Case 6	26, F	Two cusps of pulmonary valve united, division rudimentary	"Phthisis pulmonalis"	Denied	Not recorded	"Primary dementia"
de Vries,[13] 1918 Case 7	.....	Fibrinous pericarditis; bicuspid pulmonary valve; right cusp larger than normal, left smaller; border slightly thickened	Not given	Not recorded	Not recorded	.....
de Vries,[13] 1918 Case 8	10, M	Heart 150 gm.; bicuspid pulmonary valve; right cusp larger than normal, left smaller, both normal	Drowning	Not recorded	Not recorded	.....
Wauchope,[14] 1928 Case 9	54, M	Bicuspid pulmonary valve; partial fusion anterior and left posterior aortic cusps; double inferior vena cava; bronchopneumonia	Head injury, pneumonia	Not recorded	Not recorded	.....
Wauchope,[14] 1928 Case 10	75, M	Bicuspid pulmonary valve; no acquired condition of heart	Pneumonia	Not recorded	Not recorded	.....
Schwartz, Shelling,[15] 1931 Case 11	22, F	Heart 600 gm.; fibrinous pericarditis; hypertrophy all chambers; left posterior and anterior cusps of pulmonary valve fused; right posterior cusp massive calcified nodule; rheumatic involvement of mitral and tricuspid	Heart failure	Congestive heart failure, auricular fibrillation, hemiplegia	Heart enlarged to left; loud systolic and long rumbling diastolic murmurs near apex, prolonged loud diastolic second left interspace radiating widely; absent P_2; increased activity pulmonary area	"Rheumatic valvulitis superimposed on malformation of pulmonary valve (absence of one leaflet)"
Ingham,[16] 1938 Case 12	23, M	Bicuspid pulmonary valve and dilatation of pulmonary artery	Leukemia	Denied	Not recorded	.....

TABLE II (*Continued*)

Author, Date and Case No.	Age and Sex	Pathologic Findings	Cause of Death	Cardiac Symptoms	Signs	Comments
Koletsky,[8] 1941 ..... Case 13	58,* M	Heart 450 gm.; hypertrophied and dilated; congenital bicuspid pulmonary valve; two normal equal cusps, competent	Uremia	Hypertension, arteriosclerosis; no cardiac symptoms	Heart enlarged; no murmurs described	.....
Koletsky,[8] 1941 ..... Case 14	56, M	Heart 600 gm.; hypertrophied and dilated; bicuspid pulmonary valve; one large posterior cusp and small anterior; competent	Bronchopneumonia	Denied	Heart enlarged; no murmurs described	.....
Edwards,[17] 1953 ..... Case 15	63, F	Congenital bicuspid pulmonary valve in orifice revealing no abnormality	Bronchopneumonia	Denied	No clinical evidence of pulmonary valvular dysfunction or heart failure	.....
Ford et al. 1954 ..... Case 16	44, F	Heart 365 gm.; hypertrophy and dilatation of right ventricle; bicuspid pulmonary valve, hypoplasia of cusps	Unknown; possible cardiac arrhythmia	Healed pulmonary tuberculosis; congestive failure, controlled	Increased activity pulmonary region; P_2 absent; rough loud diastolic and systolic murmurs; same area, transmitted to apex	.....

* Patient Negro.

cases. Five of these patients had neither cardiac symptoms nor associated disease of the heart or lungs. Six had both congestive failure and associated disease, that is, two patients had rheumatic heart disease, one had multiple aortic aneurysms, one had bacterial endocarditis and two patients had chronic pulmonary disease. Our patient was free from symptoms of congestive failure until convalescing from extensive pulmonary tuberculosis. At this time x-rays (Figs. 1 and 2) showed increasing pulmonary fibrosis. It is possible that consequent reduction of the pulmonary capillary bed offered increased resistance to pulmonary blood flow, increasing the regurgitation through the incompetent pulmonary valve, and leading to right-sided heart failure. We may conclude that a bicuspid pulmonary valve, even if anatomically incompetent, does not lead to congestive heart failure unless additional strain is imposed on the heart by other chronic disease of heart or lungs. This conclusion agrees with experimental studies. Barger and associates produced pulmonary insufficiency in dogs but were unable to precipitate congestive heart failure even after subjecting the animals to months of strenuous exercise.[20]

Physical findings are reported in ten cases. In four of these a diastolic murmur was heard which could have been interpreted as evidence of pulmonary regurgitation. This diagnosis was suspected antemortem only in Case 11 and in the present case. Thus a bicuspid valve may be competent and give no clinical clue to its presence or it may, as in the present case, present a distinct clinical picture of pulmonary valvular insufficiency.

Pulmonary Valvular Insufficiency. The evidence for pulmonary insufficiency in this case consists of the physical findings, the contour of pulmonary artery pressure curves, the anatomic incompetence of the pulmonary valve and the area of endocardial thickening at the site of the regurgitant stream.

The causes of pulmonary valvular insufficiency are given a comprehensive classification by Friedberg[21] as follows:

I. Acquired Pulmonary Insufficiency
  A. Organic
    1. Bacterial endocarditis
    2. Rheumatic fever
    3. Pulmonary arteritis and valvulitis secondary to aortic aneurysm
    4. Syphilis of pulmonary artery
  B. Functional (pulmonary hypertension)
    1. Mitral stenosis
    2. Bronchopulmonary disease
    3. Primary pulmonary sclerosis
II. Congenital Pulmonary Insufficiency
  A. Deficient or supernumerary cusps
  B. Congenital dilatation of pulmonary artery

Examples of most of these conditions are reported by McGuire and McNamara.[22] No

statistics are available on the incidence of each cause. It is worth noting that in both the acquired and congenital groups pulmonary insufficiency is usually the result of or concomitant with other serious disease of the heart or lungs. Mitral stenosis is probably the most common cause of pulmonary insufficiency, while isolated bicuspid pulmonary valve must be considered one of the rarest.

Clinical picture of pulmonary insufficiency: Pulmonary insufficiency is suggested by characteristic physical findings and, as illustrated by the present case, modern diagnostic methods can establish the diagnosis conclusively. The following summary is based partly on the descriptions of White,[23] Donzelot and D'Allaines,[24] Vander Veer[25] and Gerhardt,[26] and partly on the present case.

Overlying the origin of the pulmonary artery, in the second or third left interspace adjacent to the sternum, there is found an area of increased precordial activity and a decrescendo diastolic murmur, usually transmitted to or beyond the apex, occasionally accompanied by a thrill. A systolic murmur may be present. The pulmonary second sound may be accentuated, normal or absent, depending on the underlying cause of the insufficiency. When pulmonary insufficiency is secondary to pulmonary hypertension, the second sound is accentuated; when due to destruction (bacterial endocarditis) or deficient development, the second sound is decreased or absent. Gerhardt describes an auscultatory finding based on the wide pulmonary capillary pulse of pulmonary insufficiency: During a slow expiration, with the stethoscope placed over the lungs, but remote from the heart, the breath sounds vary in intensity with ventricular systole and diastole.

The physical findings of pulmonary insufficiency are to be distinguished from those of aortic insufficiency or aortic-pulmonary window. The aortic murmurs are usually located slightly lower and to the left and are often associated with peripheral signs of aortic insufficiency and left ventricular hypertrophy.

Diagnostic methods: The electrocardiogram in pulmonary insufficiency may show right ventricular hypertrophy if the regurgitant stream is large enough or if pulmonary hypertension is present. In the present case the electrocardiogram showed early right ventricular hypertrophy, and prominent P waves indicated right atrial hypertrophy.

Phonocardiograms showed a typical decrescendo diastolic murmur. (Fig. 5.)

X-ray and fluoroscopic findings are more helpful. They demonstrate prominence of the pulmonary conus and artery with markedly increased pulsation of the pulmonary artery or "hilar dance."[27] This phenomenon is the most characteristic evidence of pulmonary insufficiency. It may be easily demonstrated by roentgenkymograms. Dilatation of the pulmonary artery may be present in any condition in which there is increased pulmonary blood flow, and in poststenotic and idiopathic dilatation as well. Hilar dance is found in other conditions in which abnormally wide pulsations are transmitted to the pulmonary artery, such as patent ductus and Lutembacher's syndrome, so that the diagnosis of pulmonary insufficiency cannot be made positively by radiographic methods alone. Curves have been obtained by electrokymography over the pulmonary artery in pulmonary insufficiency which are similar to those obtained from the aorta in aortic insufficiency and which resemble direct pressure tracings in contour.[28]

Pressure curves* obtained from the right ventricle and pulmonary artery are presented in Figure 11. Systolic pressure is the same in both areas. The curves illustrated suggest that end diastolic pressure may be slightly higher in the pulmonary artery than in the ventricle. On the other hand, the average values for end diastolic pressure in Table 1 are not significantly different in the two areas. These figures represent averages of ten successive cycles, or two respiratory cycles. End diastolic pressure is measured at the onset of ventricular pressure rise, 0.09 seconds after onset of the QRS complex. Thus diastolic pressure in the pulmonary artery drops to or very close to the level of diastolic pressure in the ventricle, producing the wide pulse pressure characteristic of regurgitation.

The shape of the pulmonary artery pressure curve has certain characteristics which resemble those of the curve of aortic insufficiency.[29] Early on the ascending limb there occurs a notch or hesitation in pressure rise. Wiggers[30] has observed this in aortic insufficiency and suggests that it may represent a momentary pressure change as the mass of blood in the ventricle begins to accelerate. An incisura appears in the

* A No. 7 catheter was used with a Sanborn inductance type electromanometer and a Sanborn Twin-Viso direct writing cardiograph.

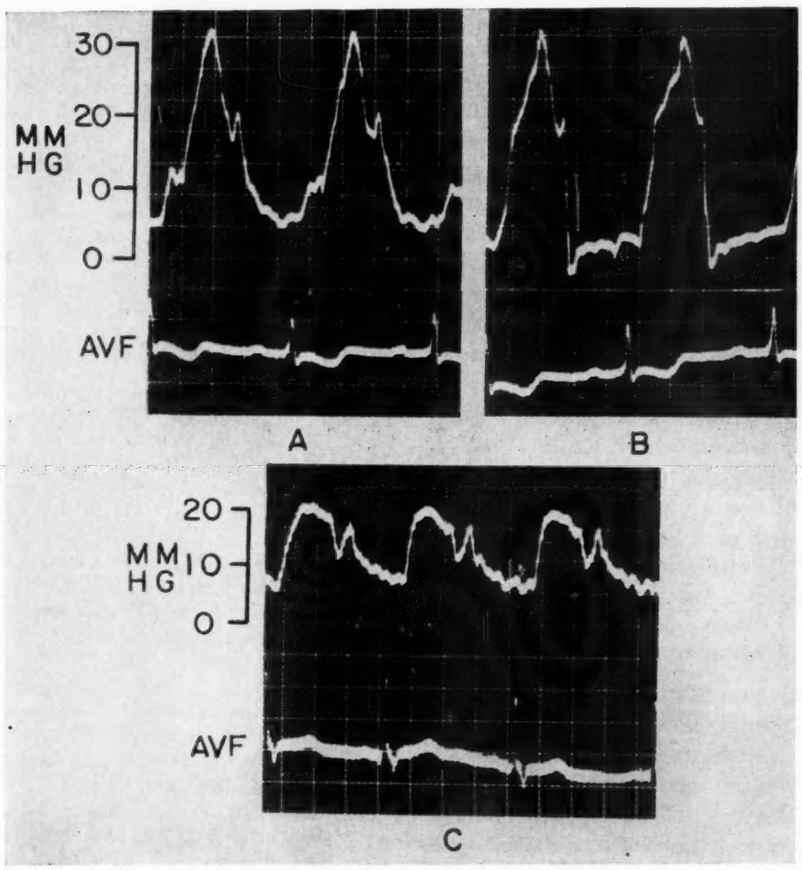

FIG. 11. Pressure curves recorded at cardiac catheterization. A, patient, pulmonary artery; B, patient, right ventricle; C, normal subject, pulmonary artery. (Discussed in text.)

pulmonary artery curve indicating that partial closure of the valves does take place. The fall of pulmonary artery pressure is momentarily delayed but its drop is much steeper than that normally observed (Fig. 11C), and the end diastolic pressure again approaches that in the ventricle. The period of systole, measured from the beginning of pressure rise in the ventricle to the sudden drop representing closure of the pulmonary valve, averages 0.38 seconds or 44 per cent of the total cycle at a rate of 68 beats per minute. The normal value for man is given as 0.27 seconds or 34 per cent of the total cycle at a rate of 75.[31] If the rates are equal the difference is even more marked, since slowing lengthens diastole but not systole. Thus it appears that the duration of systole relative to the total cycle length is increased. This has also been found in experimental aortic insufficiency.

A report of cardiac catheterization findings in a case of pulmonary insufficiency has been published by Giraud et al.[32] The pattern is very similar to that found in the present case except that there is evidence of pulmonary stenosis and elevated pressure in both right ventricle and pulmonary artery. The diagnosis had not been confirmed anatomically at the time of publication. Observations on catheterization which are consistent with pulmonary insufficiency in at least one case following open pulmonary valvuloplasty are presented by Blount et al.[33]

SUMMARY

A case of isolated bicuspid pulmonary valve is presented in detail. Congestive heart failure developed following the healing of pulmonary tuberculosis with diffuse fibrosis. The diagnosis of pulmonary valvular insufficiency was made clinically and by cardiac catheterization and was confirmed at autopsy.

Bicuspid pulmonary valve is often part of a major anomaly but is rare alone; in the present case it is considered congenital. Fifteen additional cases are collected from the literature. The

prognosis is relatively good; average age of the patient at death was 43.9 years. Six of fifteen patients died of causes indirectly related to the anomaly. There were two subjects with bacterial endocarditis and one with rheumatic pulmonary valvulitis. Six of eleven patients developed congestive heart failure but only in the presence of additional disease of heart or lungs. A diastolic murmur was present in four patients out of ten.

This anomaly is one of the rarest causes of pulmonary insufficiency. If a diastolic murmur is present, pulmonary insufficiency may be suspected clinically. X-ray, fluoroscopy, roentgenkymograms and electrokymograms demonstrate the wide pulse pressure of pulmonary insufficiency. A definitive diagnosis depends on the contour of pulmonary artery pressure curves obtained by cardiac catheterization. These curves are closely comparable with those of aortic insufficiency.

ADDENDUM

Since this article was submitted for publication a report of catheterization findings consistent with pulmonary insufficiency has been reported by S. R. Kjellberg et al. (Diagnosis of Congenital Heart Disease, Chicago, 1955. Year Book Publishers, Inc.) The case was that of a seven year old boy with a pulmonary diastolic murmur but without abnormalities of electrocardiogram or x-ray. The pressure curves are very similar to those presented in this article.

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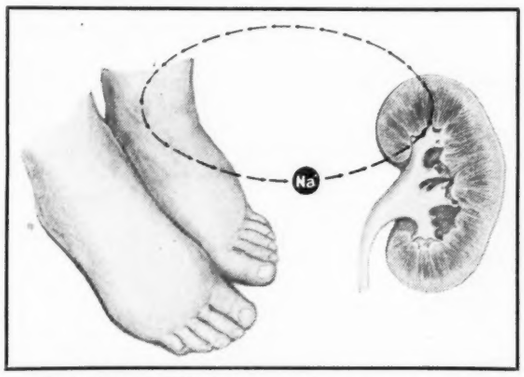

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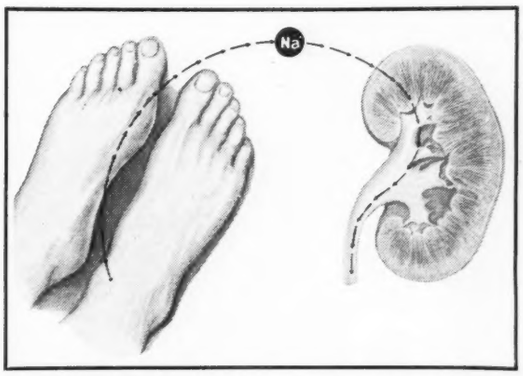

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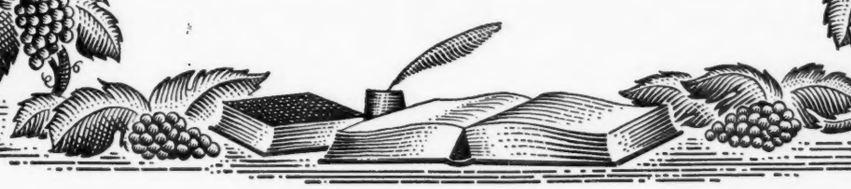

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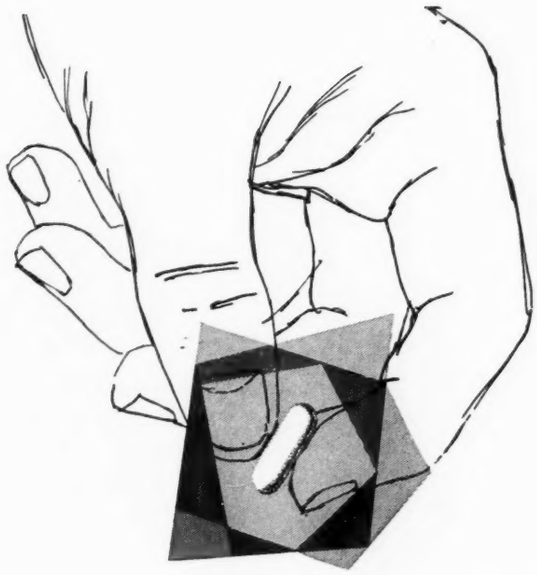

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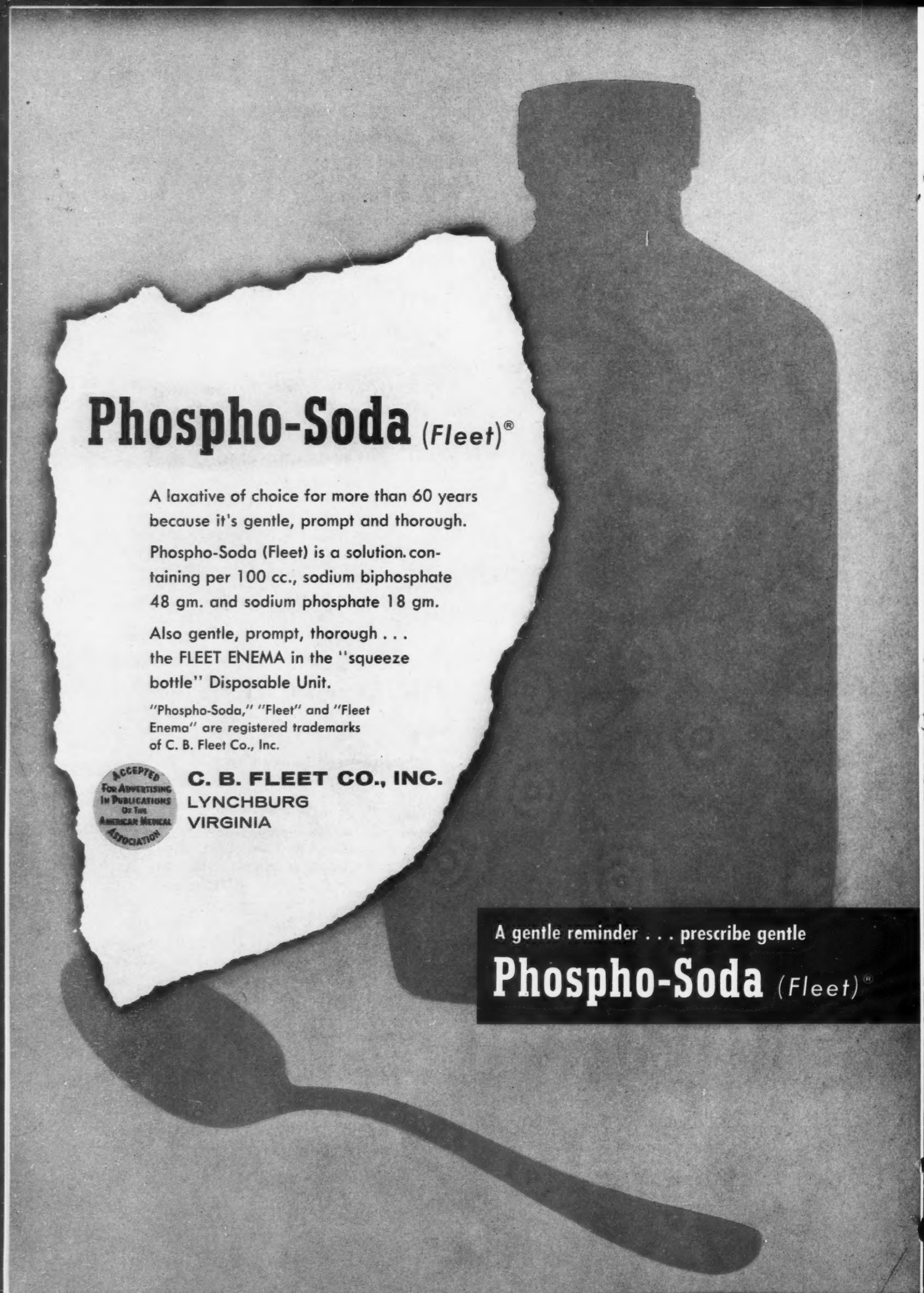
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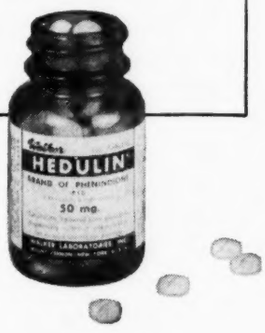

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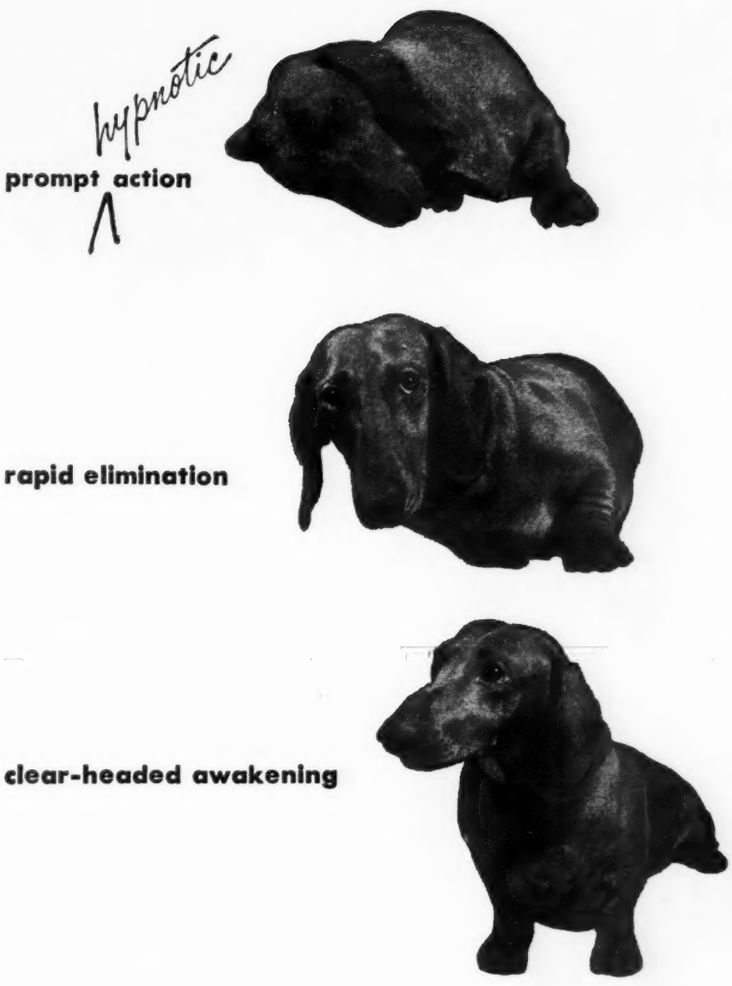

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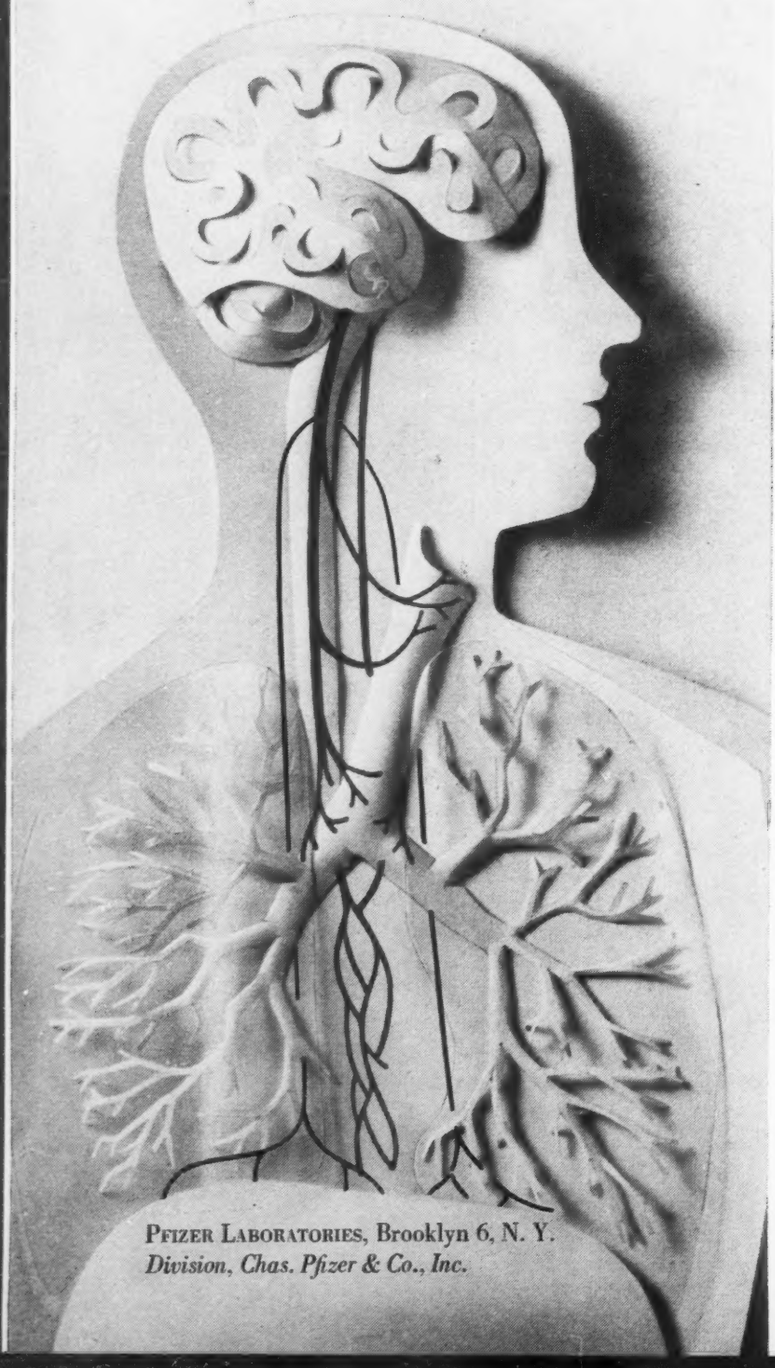

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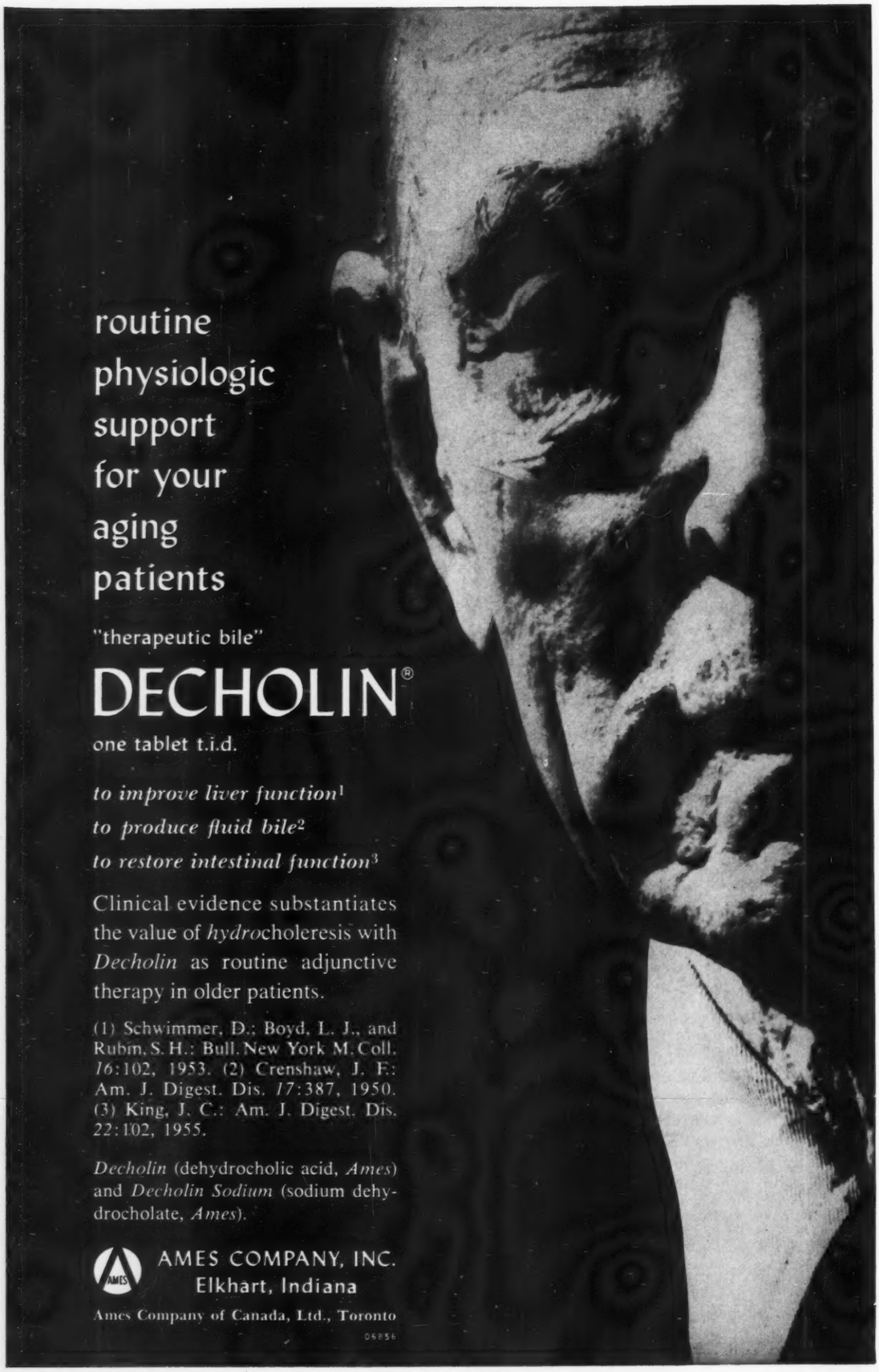
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(1) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. 16:102, 1953. (2) Crenshaw, J. F.: Am. J. Digest. Dis. 17:387, 1950. (3) King, J. C.: Am. J. Digest. Dis. 22:102, 1955.
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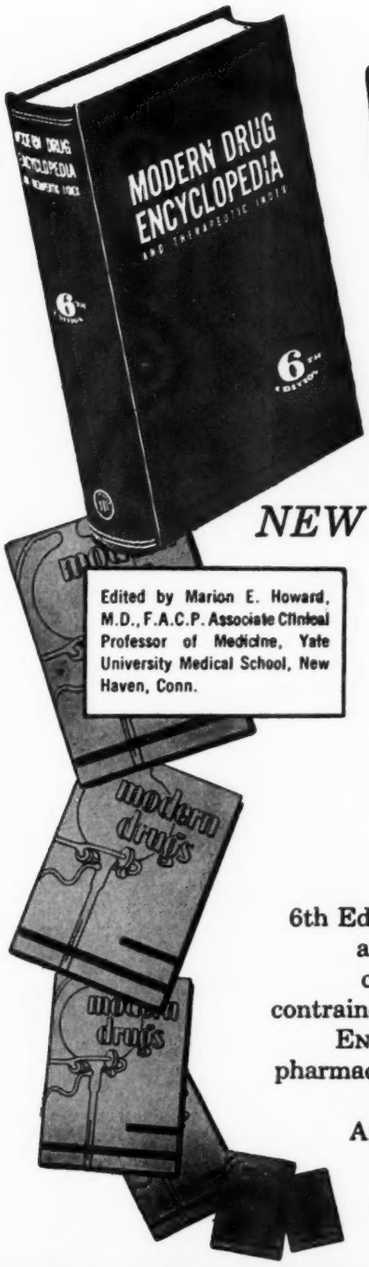

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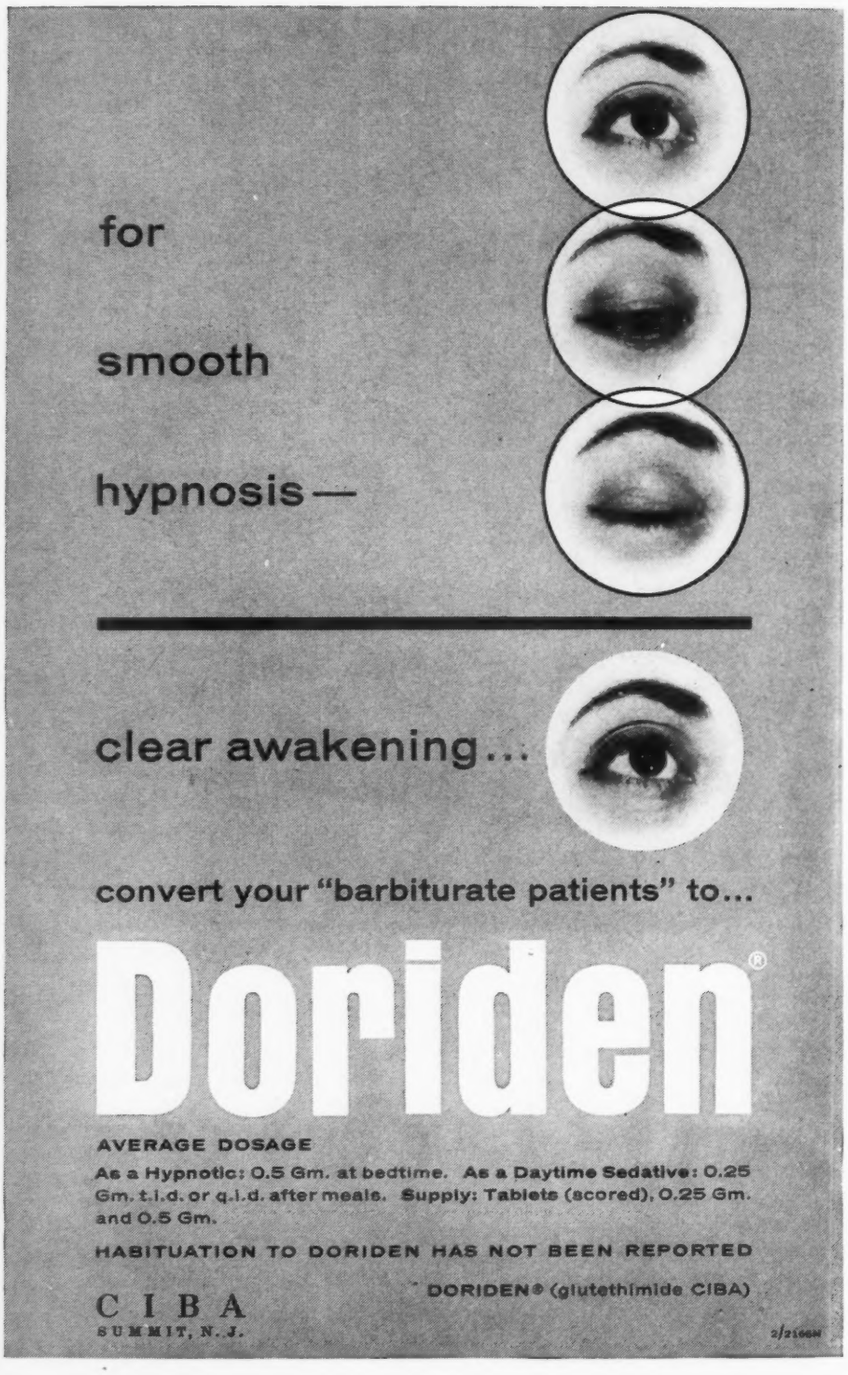
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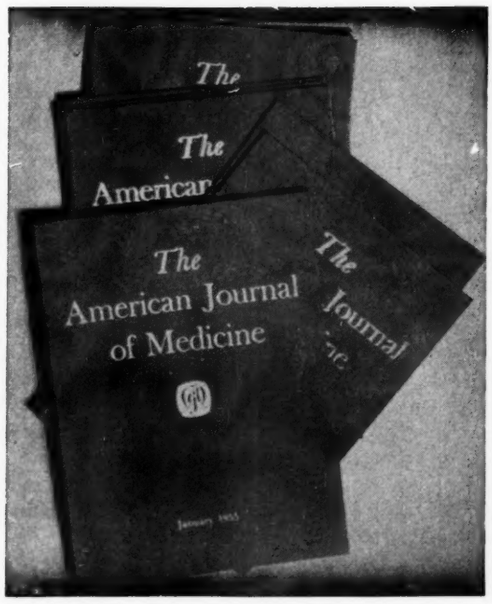

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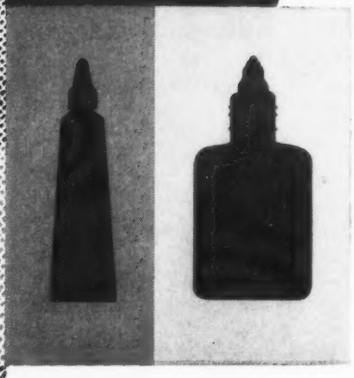

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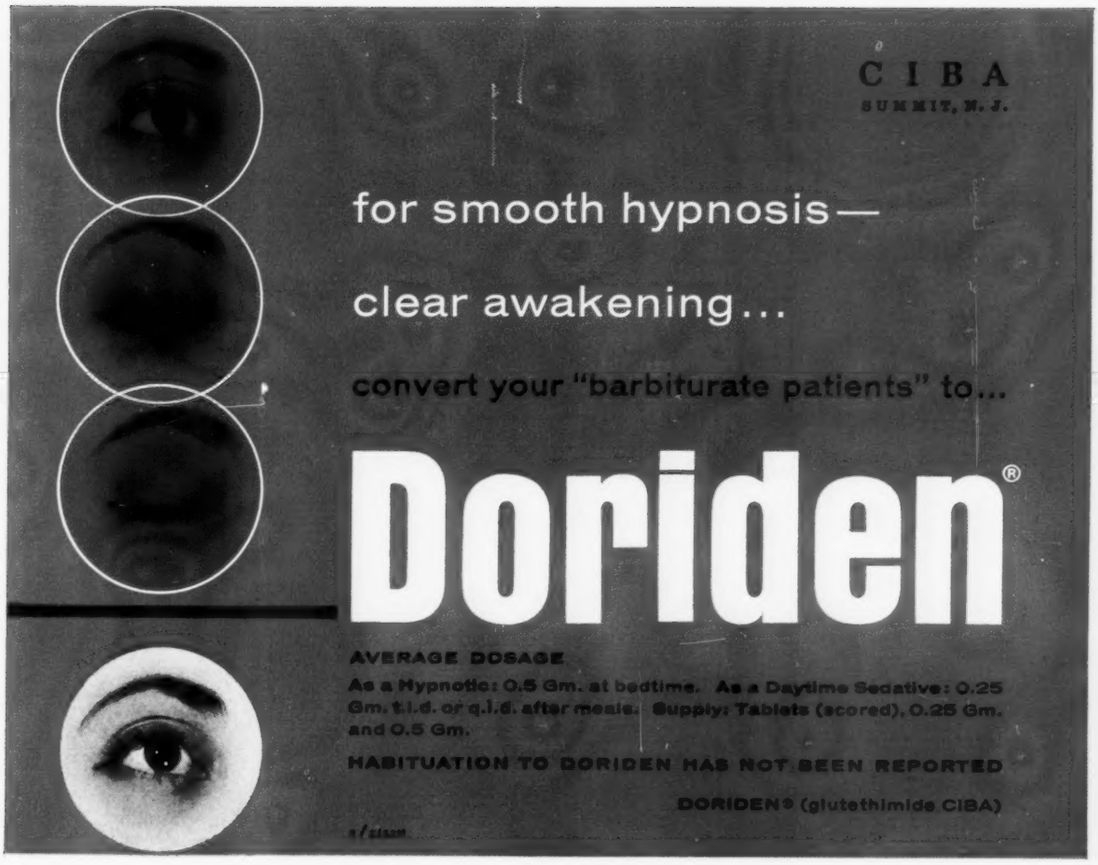
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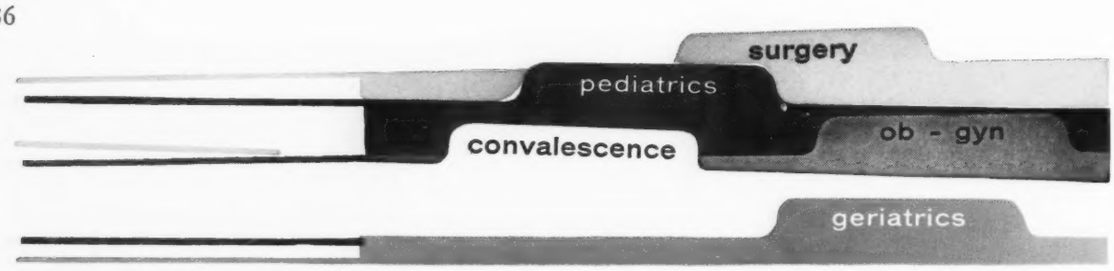

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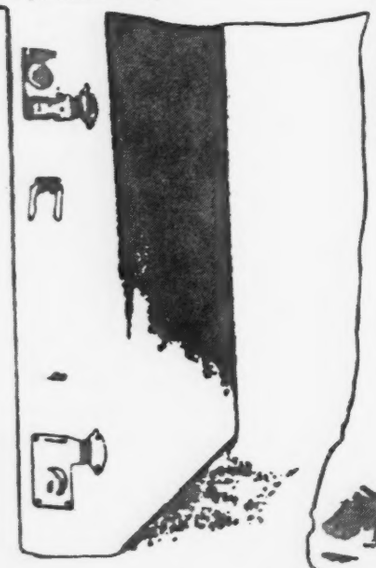

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